No. 2022-2217

United States Court of Appeals
for the Federal Circuit

UNITED THERAPEUTICS CORPORATION,

Plaintiff-Appellee,

v.

LIQUIDIA TECHNOLOGIES, INC.,

Defendant-Appellant.

Appeal from the United States District Court for the District of Delaware, No. 20-755, Judge Richard Andrews

DEFENDANT-APPELLANT'S MOTION TO EXPEDITE BRIEFING AND ORAL ARGUMENT

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UNITED STATES COURT OF APPEALS
FOR THE FEDERAL CIRCUIT

CERTIFICATE OF INTEREST

Case Number 22-2217

Short Case Caption United Therapeutics Corporation v. Liquidia Technologies, Inc.

Filing Party/Entity Liquidia Technologies, Inc.

Instructions: Complete each section of the form. In answering items 2 and 3, be specific as to which represented entities the answers apply; lack of specificity may result in non-compliance. **Please enter only one item per box; attach additional pages as needed and check the relevant box**. Counsel must immediately file an amended Certificate of Interest if information changes. Fed. Cir. R. 47.4(b).

I certify the following information and any attached sheets are accurate and complete to the best of my knowledge.

Date: 09/27/2022

Signature: /s/ Sanya Sukduang

Name: Sanya Sukduang

1. Represented Entities. Fed. Cir. R. 47.4(a)(1).	**2. Real Party in Interest.** Fed. Cir. R. 47.4(a)(2).	**3. Parent Corporations and Stockholders.** Fed. Cir. R. 47.4(a)(3).
Provide the full names of all entities represented by undersigned counsel in this case.	Provide the full names of all real parties in interest for the entities. Do not list the real parties if they are the same as the entities. ☑ None/Not Applicable	Provide the full names of all parent corporations for the entities and all publicly held companies that own 10% or more stock in the entities. ☐ None/Not Applicable
Liquidia Technologies, Inc.		Liquidia Corporation

☐ Additional pages attached

4. Legal Representatives. List all law firms, partners, and associates that (a) appeared for the entities in the originating court or agency or (b) are expected to appear in this court for the entities. Do not include those who have already entered an appearance in this court. Fed. Cir. R. 47.4(a)(4).

☐ None/Not Applicable ☐ Additional pages attached

Sanya Sukduang, Cooley LLP	Erik B. Milch, Cooley LLP	
Deepa Kannappan, Cooley LLP	Jonathan Davies, Cooley LLP	

5. Related Cases. Provide the case titles and numbers of any case known to be pending in this court or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal. Do not include the originating case number(s) for this case. Fed. Cir. R. 47.4(a)(5). See also Fed. Cir. R. 47.5(b).

☐ None/Not Applicable ☐ Additional pages attached

United Therapeutics Corporation v. Liquidia Technologies, Inc., IPR2020-00770	United Therapeutics Corporation v. Liquidia Technologies, Inc. (Fed. Cir.) No. 22-2174	
United Therapeutics Corporation v. Liquidia Technologies, Inc., IPR2021-00406		
United Therapeutics Corporation v. Liquidia Technologies, Inc. (Fed. Cir.) No. 22-2133		

6. Organizational Victims and Bankruptcy Cases. Provide any information required under Fed. R. App. P. 26.1(b) (organizational victims in criminal cases) and 26.1(c) (bankruptcy case debtors and trustees). Fed. Cir. R. 47.4(a)(6).

☑ None/Not Applicable ☐ Additional pages attached

Pursuant to Federal Rule of Appellate Procedure 2 and Federal Circuit Rule 27(c), Defendant-Appellant Liquidia Technologies, Inc. ("Liquidia") respectfully moves the Court to expedite briefing and oral argument in this matter.[1] In accordance with Federal Circuit Rule 27(a)(2), counsel for Liquidia discussed this motion with counsel for Plaintiff-Appellee United Therapeutics Corporation ("UTC") to seek their consent. UTC indicated that it would oppose this motion and intends to file a response.

BACKGROUND

Liquidia is an innovative pharmaceutical company that has utilized its own proprietary PRINT® technology to formulate treprostinil into a powder formulation that can be administered utilizing a dry powder inhaler ("DPI") for the treatment of pulmonary arterial hypertension ("PAH"). Based on its research and development, Liquidia filed a New Drug Application No. 213005 under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act with the Food and Drug Administration (the "FDA") on January 24, 2020, for YUTREPIA™ (formerly known as LIQ861). Liquidia's NDA included "Paragraph IV" certifications pursuant to 21 U.S.C. § 355(b)(2)(A)(iv), indicating that U.S. Patent Nos. 9,593,066 (the "'066 patent"), 9,604,901 (the "'901 patent"), and 10,716,793 (the "'793 patent") were invalid and

[1] Liquidia has also filed a similar motion to expedite in companion Case Nos. 2022-2133, 2022-2174.

not infringed. UTC filed suit in the District of Delaware on June 4, 2020, and UTC later amended its complaint on July 22, 2020 to assert infringement of the '793 patent ("the District Court Action"). Ex. 1 at 1, ¶ 1. The FDA tentatively approved Liquidia's NDA No. 213005 on November 5, 2021. Ex. 2 at 1.

Trial was held in the District Court Action at the end of March 2022, and the district court issued its opinion on August 31, 2022, finding all asserted claims of the '066 patent either invalid or not infringed (asserted claims 1, 2, 3, 6, and 9 of the '066 patent invalid, asserted claims 6, 8 and 9 of the '066 patent not infringed) and asserted claims 1, 4, and 6-8 of the '793 patent valid and infringed. *See* Ex. 3 at 16, 17, 25, 34, 45, 48, 53. The district court entered judgment on September 9, 2022, resetting the date of Final FDA approval until expiration of the '793 patent. Ex. 4 at 2, ¶ 4. Liquidia filed a motion, pursuant to Federal Rule of Civil Procedure 62, to partially stay enforcement of judgment until resolution of this appeal. Liquidia's motion is still pending before the district court.

In parallel proceedings before the Patent Trial and Appeal Board, Liquidia initiated *inter partes* review ("IPR") proceedings against the '901 and '793 patents. On October 8, 2021, the PTAB issued its Final Written Decision ("FWD") with respect to the '901 patent, construing certain claim limitations and determining that asserted claims 1-5, 8, and 9 were unpatentable as obvious over the prior art. Ex. 5 at 2. Following the PTAB's decision and the district court's adoption of certain

PTAB constructions, UTC stipulated in the District Court Action to non-infringement of the asserted claims of the '901 patent. Ex. 6.

Similarly, on July 19, 2022, the PTAB issued its FWD with respect to the '793 patent, rendering unpatentable all claims of the '793 patent as obvious over the prior art. Ex. 7 at 2, 46-47. On August 18, 2022, UTC filed a Request for Rehearing, which is still pending.

Despite the PTAB's '793 FWD invalidating all asserted claims issuing prior to the district court's opinion in the District Court Action, the district court nonetheless concluded, contrary to the Supreme Court's decision in *Commil USA, LLC v. Cisco Sys, Inc.,* 575 U.S. 632 (2015), that Liquidia possessed the specific intent to induce infringement under 35 U.S.C. § 271(b). Ex. 3 at 36-37. Accordingly, the district court enjoined the FDA from granting "final" approval to YUTREPIA™, based solely on a patent that has been rendered unpatentable. Ex. 4 at 2, ¶ 4. Without final FDA approval, Liquidia cannot launch YUTREPIA™, thereby preventing PAH patients from having access to this innovative, life-saving drug. The only way to avoid further harm to Liquidia and PAH patients is for this Court to expedite briefing and hear oral arguments as soon as possible. As such,

Liquidia respectfully requests the Court enter the following expedited schedule for Case No. 2022-2217[2]:

Filing	Expedited Due Date
Defendant-Appellant's Opening Briefs	10/14/2022
Plaintiff-Appellee's Responsive Briefs	11/03/2022
Defendant-Appellant's Reply Briefs	11/23/2022
Oral Argument	Next available date after briefing is complete

ARGUMENT

This Court has authority to manage its docket to expedite appeals upon a showing of good cause. Fed. R. App. P. 2; Fed. Cir. R. 27. As discussed herein, good cause to expedite briefing, oral argument, and final resolution of this appeal exists because the district court enjoined the FDA from granting final approval for YUTREPIA™, preventing its launch, based solely on a patent that was rendered unpatentable by the PTAB.

Although the district court held the '793 patent valid and infringed, a conflicting decision on validity of that patent was issued by the PTAB prior to the district court's opinion. While Liquidia has filed a motion to partially stay enforcement of the District Court Action's judgment and injunction, the district court has not yet issued a decision. As such, until this appeal and the appeal in companion

[2] Liquidia has requested this Court enter the same expedited schedule for companion Case Nos. 2022-2133, 2022-2174.

Case Nos. 2022-2133, 2022-2174 are resolved, UTC is able to use the district court's decision on the '793 patent to restrict competition by keeping Liquidia's YUTREPIA™ product off the market.

A basic tenet of Hatch-Waxman proceedings is to promote competition by permitting prompt resolution of patent infringement proceedings of Orange Book listed patents. *See Caraco Pharm. Lab'ys Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 405 (2012). While the *Caraco* case concerned generic drugs, the same rationale applies here as Liquidia was required to follow the Hatch-Waxman regulatory schedule because it filed its NDA under § 505(b)(2). Expediting this appeal will achieve this goal.

Expediting this appeal is particularly warranted here, given the PTAB's decision rendering unpatentable all asserted claims of the '793 patent. As Congress noted, in enacting the America Invents Act, "questionable patents [we]re too easily obtained and [were] too difficult to challenge[,]" and IPR proceedings combat this by "providing a more efficient system for challenging patents that should not have issued." H.R. Rep. No. 112-98 at 38-40 (2011). Liquidia acted in accordance with IPR procedures, prevailed in invalidating the '793 patent claims, but is nonetheless prohibited from obtaining final FDA approval because the district court reached a different decision, which failed to properly take into account the PTAB's decision. *See Commil*, 575 U.S. at 642, 635, 644-45 (holding that "if [a] patent is indeed

invalid, and shown to be so under the proper procedures, there is no liability" and identifying "*inter partes* review at the Patent Trial and Appeal Board," where a defendant can "receive a decision as to validity within 12 to 18 months" as a "proper procedure").

Liquidia has also acted diligently in bringing this appeal and the cross-appeal in companion Case Nos. 2022-2133, 2022-2174. Liquidia timely filed its notice of appeal of the District Court Action on September 12, 2022, which is three days after the district court issued its final judgment. *See* ECF No. 1-2. In parallel, UTC filed its notice of appeal of the PTAB's '901 FWD on August 15, 2022, Liquidia filed its cross-appeal on August 29, 2022, and the appeals were consolidated on September 1, 2022. *United Therapeutics Corp. v. Liquidia Techs., Inc.*, Case Nos. 2022-2133, 2022-2174, ECF No. 1-2, ECF No. 6. Case No. 2022-2217 and Case Nos. 2022-2133, 2022-2174 were designated as companion cases on September 19, 2022. ECF No. 2; Case Nos. 2022-2133, 2022-2174, ECF No. 18. On September 21, 2022, two days after the appeals were designated as companion cases, Liquidia sought UTC's consent to expedite the schedule, the parties conferred on September 23, and UTC indicated on September 26 that it would not consent. Even without a formal order expediting the briefing schedule, Liquidia has accelerated the deadlines it controls. Fed. Cir. R. 4 (Prac. Notes). A formal order expediting this appeal is nonetheless needed as UTC has the ability to delay ultimate resolution, including by seeking

extensions of time of its own deadlines in the appeals. Fed. R. App. P. 4(a)(5), 26(b); Fed. Cir. R. 26(b).

Finally, UTC will not suffer prejudice if the briefing schedule is expedited. The district court has already issued its final judgment enjoining the FDA from granting Liquidia final approval, and YUTREPIA™ is not on the market. And while UTC's deadlines will be advanced, it is currently represented by multiple law firms, ensuring that UTC will not have an issue meeting these deadlines. Case Nos. 2022-2133, 2022-2174, ECF Nos. 11, 16. Finally, during the parties' conference addressing Liquidia's request to expedite the appeal schedule, UTC did not indicate it would be prejudiced by expediting the schedule.

CONCLUSION

For the foregoing reasons, Defendant-Appellant Liquidia, respectfully requests that the Court expedite briefing and oral argument in Case No. 2022-2217, in accordance with the following schedule:

Filing	Expedited Due Date
Defendant-Appellant's Opening Briefs	10/14/2022
Plaintiff-Appellee's Responsive Briefs	11/03/2022
Defendant-Appellant's Reply Briefs	11/23/2022
Oral Argument	Next available date after briefing is complete

Pursuant to Federal Circuit Rule 27(c)(2), Liquidia further proposes the following briefing schedule on this motion:

Filing	Expedited Due Date
Defendant-Appellant's Opening Motion	9/27/2022
Plaintiff-Appellee's Response to Motion	10/04/2022
Defendant-Appellant's Reply to Response	10/07/2022

Dated: September 27, 2022

Respectfully submitted,

/s/ Sanya Sukduang

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CERTIFICATE OF COMPLIANCE

The foregoing filing complies with the type-volume limitation of Federal Rule of Appellate Procedure 27(d) and 32(a) and has been prepared using a proportionally-spaced typeface and includes 1,571 words.

Dated: September 27, 2022

/s/ Sanya Sukduang
Sanya Sukduang
Cooley LLP

Counsel for Defendant-Appellant Liquidia Technologies, Inc.

LIST OF EXHIBITS

Ex. 1	*United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-755, ECF No. 16, First Amended Complaint (D. Del. July 22, 2020)
Ex. 2	Tentative Approval Letter for New Drug Application No. 213005 (Nov. 5, 2021)
Ex. 3	*United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-755, ECF No. 433, Trial Opinion (D. Del. Aug. 31, 2022)
Ex. 4	*United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-755, ECF No. 436, Final Judgment (D. Del. Sept. 9, 2022)
Ex. 5	*Liquidia Techs., Inc. v. United Therapeutics Corp.*, IPR2020-00770, Paper 45 (P.T.A.B. Oct. 8, 2021)
Ex. 6	*United Therapeutics Corp. v. Liquidia Techs., Inc.*, No. 20-755, Dkt. No. 278, Stipulation of Partial Judgment of Non-Infringement and Order (D. Del. Jan. 3, 2022)
Ex. 7	*Liquidia Techs., Inc. v. United Therapeutics Corp.*, IPR2021-00406, Paper 78 (P.T.A.B. Jul. 19, 2022)

EXHIBIT 1

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)	
Plaintiff,	)	
v.	)	C.A. No. 20-755 (RGA)
LIQUIDIA TECHNOLOGIES, INC.,	)	
Defendant.	)	

FIRST AMENDED COMPLAINT

Plaintiff United Therapeutics Corporation ("UTC"), by its undersigned attorneys, for its First Amended Complaint against Liquidia Technologies, Inc. ("Liquidia"), alleges as follows:

NATURE OF THE ACTION

1. This is an action for patent infringement arising under the patent laws of the United States, Title 35, United States Code, Sections 100 *et seq.*, involving United States Patent Nos. 9,593,066 ("the '066 patent") (attached as Exhibit A hereto), 9,604,901 ("the '901 patent") (attached as Exhibit B hereto), and 10,716,793 ("the '793 patent") (attached as Exhibit C hereto) (collectively, the "Patents-in-Suit").

2. This action arises out of Liquidia's submission of New Drug Application No. 213005 under § 505(b)(2) of the Federal Food, Drug and Cosmetic Act ("Liquidia's 505(b)(2) Application") to the United States Food and Drug Administration ("FDA") seeking approval, prior to the expiration of the '066 patent, the '901 patent, and the '793 patent, to manufacture, market, and sell a generic copy of UTC's TYVASO® (treprostinil) Inhalation Solution, 0.6 mg/ml that is approved by FDA for treatment of pulmonary arterial hypertension ("Liquidia's Proposed Generic Product").

THE PARTIES

3. UTC is a corporation organized and existing under the laws of the State of Delaware and having a place of business at 1040 Spring Street, Silver Spring, Maryland 20910. UTC is a biotech company focused on the development and commercialization of products designed to address the needs of patients with chronic and life-threatening conditions. UTC continues to research and develop treatments for cardiovascular and pulmonary diseases, pediatric cancers, and other orphan diseases.

4. Upon information and belief, Liquidia is a corporation organized and existing under the laws of the State of Delaware, with a registered office at 51 Little Falls Drive, Wilmington, Delaware 19808, and a principal place of business at 419 Davis Drive, Suite 100, Morrisville, North Carolina 27560.

5. Upon information and belief, to manufacture Liquidia's Proposed Generic Product, Liquidia purchases the treprostinil sodium active pharmaceutical ingredient ("API") from third-party manufacturer Yonsung Fine Chemicals Co., LTD ("Yonsung"), operating out of South Korea. Upon information and belief, Liquidia will import treprostinil sodium API from Yonsung into the United States.

6. Upon information and belief, Liquidia's Proposed Generic Product delivers treprostinil through a dry powder inhaler ("DPI") that is manufactured by Plastiape SpA ("Plastiape"). Upon information and belief, Plastiape has a principal place of business at Via Primo Maggio, 8 Osnago, 23875 Italy. Upon information and belief, Plastiape is a wholly-owned subsidiary of Berry Global Group, Inc. Upon information and belief, Berry Global Group, Inc. has a principal place of business at 101 Oakley Street, Evansville, Indiana 47710.

JURISDICTION AND VENUE

7. This Court has jurisdiction over the subject matter of this action pursuant to the provisions of 28 U.S.C. §§ 1331, 1338(a), 2201, and 2202.

8. Venue is proper in this Court under 28 U.S.C. § 1400(b).

9. Upon information and belief, this Court has personal jurisdiction over Liquidia because it is a corporation organized and existing under the laws of the State of Delaware with a registered agent in the State of Delaware. Further, upon information and belief, Liquidia has publicly stated its intent to engage in commercializing Liquidia's Proposed Generic Product throughout the United States without any limitation. Upon information and belief, Liquidia will manufacture, market, distribute, and/or sell Liquidia's Proposed Generic Product throughout the United States, including in Delaware, and will derive substantial revenue therefrom. Upon information and belief, upon approval of Liquidia's 505(b)(2) Application, Liquidia will place Liquidia's Proposed Generic Product into the stream of commerce with the reasonable expectation or knowledge and the intent that such products will ultimately be purchased and used by consumers in Delaware.

BACKGROUND

10. UTC holds New Drug Application No. 022387, which has been approved for TYVASO® (treprostinil) Inhalation Solution, 0.6 mg/ml, which UTC markets and sells under the registered trademark TYVASO®.

11. TYVASO® is a pharmaceutical product initially approved by FDA in the United States in July 2009 and is indicated for the treatment of pulmonary arterial hypertension. Pulmonary arterial hypertension is a rare disease affecting the pulmonary vasculature and results

in high pressure in the pulmonary arteries, which increases strain on the right ventricle of the heart, thereby leading to heart failure and death.

12. TYVASO® is an inhalable product approved for sale in a 0.6 mg/mL concentration.

13. The '066 patent, entitled "Process to prepare treprostinil, the active ingredient in Remodulin®," was duly and legally issued by the United States Patent and Trademark Office on March 14, 2017, and is scheduled to expire on December 15, 2028. The named inventors are Hitesh Batra, Sudersan M. Tuladhar, Raju Penmasta, and David A. Walsh.

14. UTC is the lawful owner of the '066 patent by assignment of all right, title and interest in and to the '066 patent, including the right to bring infringement suits thereon.

15. The '901 patent, entitled "Process to prepare treprostinil, the active ingredient in Remodulin®," was duly and legally issued by the United States Patent and Trademark Office on March 28, 2017, and is scheduled to expire on December 15, 2028. The named inventors are Hitesh Batra, Sudersan M. Tuladhar, Raju Penmasta, and David A. Walsh.

16. UTC is the lawful owner of the '901 patent by assignment of all right, title and interest in and to the '901 patent, including the right to bring infringement suits thereon.

17. The '793 patent, entitled "Treprostinil Administration by Inhalation," was duly and legally issued by the United States Patent and Trademark Office on July 21, 2020, and is scheduled to expire on May 14, 2027. The named inventors are Horst Olschewski, Robert Roscigno, Lewis J. Rubin, Thomas Schmehl, Werner Seeger, Carl Sterritt, and Robert Voswinckel.

18. UTC is the lawful owner of the '793 patent by assignment of all right, title and interest in and to the '793 patent, including the right to bring infringement suits thereon.

19. TYVASO® and its FDA approved manufacture and uses are covered by one or more claims of the '066 patent, the '901 patent, and the '793 patent, which have been listed in connection with TYVASO® in the FDA's *Approved Drug Products with Therapeutic Equivalents* publication (also known as the "Orange Book").

ACTS GIVING RISE TO THIS ACTION

20. Liquidia notified UTC by letter dated April 24, 2020, which was delivered to UTC on or about April 27, 2020 ("Liquidia's Notice Letter"), that it had submitted NDA No. 213005 to the FDA seeking approval to engage in the commercial manufacture, use and/or sale of Liquidia's Proposed Generic Product prior to the expiration of the'066 patent and the '901 patent.

21. Liquidia's Notice Letter included a statement pursuant to 21 U.S.C. § 355(b)(3)(D)(ii) and 21 C.F.R. § 314.52(c)(6) purporting to recite Liquidia's "factual and legal basis" for its opinion that the '066 patent and the '901 patent are invalid, unenforceable, and/or are not, and will not, be infringed by the commercial manufacture, use or sale of Liquidia's Proposed Generic Product. That statement did not include anything beyond conclusory statements as to why the claims of the '066 patent and the '901 patent were allegedly invalid. The statement also did not include anything beyond conclusory statements regarding alleged non-infringement.

22. Upon information and belief, Liquidia submitted Liquidia's 505(b)(2) Application to FDA seeking approval to commercially manufacture, market, use, and sell generic copies of UTC's TYVASO® (treprostinil) Inhalation Solution, 0.6 mg/mL prior to the expiration of the '066 patent and the '901 patent.

23. UTC commenced this action before the expiration of forty-five days from the date it received Liquidia's Notice Letter.

24. Upon information and belief, Liquidia's Proposed Generic Product contains the same active compound, treprostinil, as UTC's approved TYVASO® product.

25. Upon information and belief, Liquidia's 505(b)(2) Application seeks approval from the FDA to market Liquidia's Proposed Generic Product for the same indication as UTC's approved TYVASO® product.

26. Upon information and belief, Liquidia's 505(b)(2) Application refers to and relies upon UTC's NDA No. 022387 for TYVASO® (treprostinil) Inhalation Solution, 0.6 mg/ml.

27. Upon information and belief, Liquidia intends to commercially manufacture, sell, offer for sale, and/or import Liquidia's Proposed Generic Product upon, or in anticipation of, FDA approval.

28. According to Liquidia's Notice Letter, Liquidia's 505(b)(2) Application contained a "Paragraph IV" certification pursuant to 21 U.S.C. § 355(b)(2)(A)(iv) stating that in Liquidia's opinion the '066 and the '901 patents are invalid, unenforceable, and/or would not be infringed by the commercial manufacture, use or sale of Liquidia's Proposed Generic Product.

29. Upon information and belief, as of the date of Liquidia's Notice Letter, Liquidia was aware of the statutory provisions and regulations set forth in 21 U.S.C. § 355(b)(3)(D)(ii) and 21 C.F.R. § 314.52(c)(6).

30. In Liquidia's Notice Letter, Liquidia offered confidential access to certain information regarding Liquidia's 505(b)(2) Application on the terms and conditions set forth in that letter ("Liquidia's Offer of Confidential Access"). Liquidia requested that UTC accept Liquidia's Offer of Confidential Access before receiving access to information regarding Liquidia's 505(b)(2) Application. Liquidia's Offer of Confidential Access contained sweeping, unreasonable restrictions that differ materially from restrictions found under protective orders.

For example, Liquidia's Offer of Confidential Access required that UTC's outside counsel "do not engage, either formally or informally, in any patent prosecution for UTC and/or are involved in the subject matter related to treprostinil, and/or provide any FDA counseling, litigation or other work before or involving FDA."

31. Under 21 U.S.C. § 355(c)(3)(D)(i)(III), an "offer of confidential access shall contain such restrictions . . . on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information."

32. UTC attempted to negotiate with Liquidia to obtain relevant information from Liquidia's 505(b)(2) Application under restrictions "as would apply had a protective order been issued." Those negotiations were unsuccessful. For example, Liquidia continued to insist that attorneys representing UTC and in-house counsel and the staff of such counsel agree not to be engaged in the drafting of submissions related to compositions, treatment methods, or formulations containing treprostinil to the FDA or to provide any FDA counseling related to such matters, though such restrictions have not been present in any prior protective order relating to any other UTC treprostinil-containing product, such as REMODULIN® (treprostinil) Injection. *See United Therapeutics Corp. v. Sandoz, Inc.*, 3:12-cv-01617-PGS-LHG, Protective Order, Docket No. 32 (D.N.J. Sept. 12, 2012); *United Therapeutics Corp. v. Teva Pharmaceuticals USA, Inc.*, 3:14-cv-05498-PGS-LHG, Protective Order, Docket No. 24, Discovery Confidentiality Order (D.N.J. Nov. 25, 2014); *United Therapeutics Corp. v. Sandoz, Inc.*, 3:14-cv-05499-PGS-LHG, Stipulated Protective Order and Cross Use Agreement (D.N.J. Jan. 15, 2015.). UTC objected to this provision of Liquidia's Offer of Confidential Access as unreasonable and in violation of 21 U.S.C. § 355(j)(5)(C)(i)(III).

33. UTC is not aware of any other means of obtaining information regarding Liquidia's Proposed Generic Product within the 45-day statutory period. Without such information, UTC will use the judicial process and the aid of discovery to obtain, under appropriate judicial safeguards, such information as is required to confirm its allegations of infringement and to present to the Court evidence that Liquidia's Proposed Generic Product falls within the scope of one or more claims of the '066 and '901 patents.

34. Upon information and belief, Liquidia's Proposed Generic Product is intended to deliver treprostinil through a DPI utilizing capsules in amounts from 26.5-106 mcgs of treprostinil, and doses from 26.5-212 mcgs of treprostinil. Upon information and belief, the contents of each capsule of Liquidia's Proposed Generic Product "can be inhaled in 1-2 breaths."

COUNT 1: INFRINGEMENT OF THE '066 PATENT
UNDER 35 U.S.C. § 271(e)

35. UTC repeats and realleges each of the foregoing paragraphs as if fully set forth herein.

36. Upon information and belief, Liquidia's Proposed Generic Product or an intermediate in its manufacture is covered by one or more claims of the '066 patent.

37. Liquidia had knowledge of the '066 patent when it submitted Liquidia's 505(b)(2) Application.

38. Liquidia's submission of Liquidia's 505(b)(2) Application for the purpose of obtaining approval to engage in the commercial manufacture, use and/or sale of Liquidia's Proposed Generic Product was an act of infringement of the '066 patent under 35 U.S.C. § 271(e)(2).

39. Upon information and belief, the commercial manufacture, use, offer for sale, sale and/or importation of Liquidia's Proposed Generic Product would infringe one or more claims of the '066 patent.

40. Upon information and belief, Liquidia was and is aware of the existence of the '066 patent and acted without a reasonable basis for believing that it would not be liable for infringement of the '066 patent, thus rendering this case "exceptional" under 35 U.S.C. § 285.

41. UTC will be substantially and irreparably damaged and harmed if Liquidia's infringement of the '066 patent is not enjoined by this Court. UTC does not have an adequate remedy at law.

COUNT 2: INFRINGEMENT OF THE '066 PATENT
UNDER 35 U.S.C. §§ 271(a)-(c) and (g)

42. UTC repeats and realleges each of the foregoing paragraphs as if fully set forth herein.

43. Upon information and belief, upon FDA approval of Liquidia's 505(b)(2) Application, Liquidia will engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Liquidia's Proposed Generic Product which will result in infringement of one or more claims of the '066 patent.

44. Liquidia's 505(b)(2) Application and Liquidia's intention to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Liquidia's Proposed Generic Product upon receiving FDA approval prior to the expiration of the '066 patent creates an actual and justiciable controversy with respect to infringement of the '066 patent.

45. Upon information and belief, upon FDA's approval of Liquidia's 505(b)(2) Application, Liquidia's commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Liquidia's Proposed Generic Product will directly infringe one or more

claims of the '066 patent, and will indirectly infringe by actively inducing infringement by others, under 35 U.S.C. § 271(a), 35 U.S.C. § 271(b), 35 U.S.C. § 271(c), and/or 35 U.S.C. § 271(g).

46. Upon information and belief, Liquidia's Proposed Generic Product or an intermediate in its manufacture as described in and/or directed by Liquidia's proposed labeling, Liquidia's 505(b)(2) Application, applicable drug master file ("DMF"), and/or other corporate documents for Liquidia's Proposed Generic Product would infringe one or more claims of the '066 patent.

47. Upon information and belief, Liquidia will induce others to infringe one or more claims of the '066 patent under 35 U.S.C. § 271(b) by, among other things, actively and knowingly aiding and abetting others to infringe, including, but not limited to the manufacturer of Liquidia's Proposed Generic Product, or its API, or other subsequent purchasers, distributors, or users thereof, which product or its manufacture constitutes direct infringement of one or more claims of the '066 patent. Upon information and belief, Liquidia's aiding and abetting includes Liquidia's engagement of, contracting of, and/or encouragement of others to engage in the manufacture, use, sale, or importation of infringing products pursuant to Liquidia's 505(b)(2) Application.

48. Upon information and belief, Liquidia will also contributorily infringe one or more claims of the '066 patent under 35 U.S.C. § 271(c) in that Liquidia will make, use, sell, offer to sell, and/or import Liquidia's Proposed Generic Product and/or the API thereof, which Liquidia knows has no substantial non-infringing uses. Upon information and belief, subsequent purchasers, distributors, or users thereof will also directly infringe one or more claims of the '066 patent.

49. Upon information and belief, Liquidia will also infringe one or more claims of the '066 patent under 35 U.S.C. § 271(g) by importing, selling, offering to sell or using Liquidia's Proposed Generic Product or the API or an intermediate thereof which is neither materially changed by subsequent process nor a trivial or non-essential component of another product.

50. Upon information and belief, Liquidia was and is aware of the existence of the '066 patent and acted without a reasonable basis for believing that it would not be liable for infringement of the '066 patent, thus rendering this case "exceptional" under 35 U.S.C. § 285.

51. UTC will be substantially and irreparably damaged and harmed if Liquidia's infringement of the '066 patent is not enjoined by this Court. UTC does not have an adequate remedy at law.

COUNT 3: INFRINGEMENT OF THE '901 PATENT
UNDER 35 U.S.C. § 271(e)

52. UTC repeats and realleges each of the foregoing paragraphs as if fully set forth herein.

53. Upon information and belief, Liquidia's Proposed Generic Product or an intermediate in its manufacture is covered by one or more claims of the '901 patent.

54. Liquidia had knowledge of the '901 patent when it submitted Liquidia's 505(b)(2) Application.

55. Liquidia's submission of Liquidia's 505(b)(2) Application for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, and/or offer for sale of Liquidia's Proposed Generic Product was an act of infringement of the '901 patent under 35 U.S.C. § 271(e)(2).

56. Upon information and belief, the commercial manufacture, use, offer for sale, sale and/or importation of Liquidia's Proposed Generic Product would infringe one or more claims of the '901 patent.

57. Upon information and belief, Liquidia was and is aware of the existence of the '901 patent and acted without a reasonable basis for believing that it would not be liable for infringement of the '901 patent, thus rendering this case "exceptional" under 35 U.S.C. § 285.

58. UTC will be substantially and irreparably damaged and harmed if Liquidia's infringement of the '901 patent is not enjoined by this Court. UTC does not have an adequate remedy at law.

COUNT 4: INFRINGEMENT OF THE '901 PATENT
UNDER 35 U.S.C. §§ 271(a)-(c) and (g)

59. UTC repeats and realleges each of the foregoing paragraphs as if fully set forth herein.

60. Upon information and belief, upon FDA approval, Liquidia will manufacture, market, sell, offer to sell, import, and distribute Liquidia's Proposed Generic Product which will result in infringement of one or more claims of the '901 patent.

61. Liquidia's 505(b)(2) Application and Liquidia's intention to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Liquidia's Proposed Generic Product upon receiving FDA approval of Liquidia's 505(b)(2) Application prior to the expiration of the '901 patent creates an actual and justiciable controversy with respect to infringement of the '901 patent.

62. Upon information and belief, upon FDA's approval of Liquidia's 505(b)(2) Application, Liquidia's commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Liquidia's Proposed Generic Product will directly infringe one or more

claims of the '901 patent, and will indirectly infringe by actively inducing infringement by others, under 35 U.S.C. § 271(a), 35 U.S.C. § 271(b), 35 U.S.C. § 271(c), and/or 35 U.S.C. § 271(g).

63. Upon information and belief, Liquidia's Proposed Generic Product or an intermediate in its manufacture as described in and/or directed by Liquidia's proposed labeling, Liquidia's 505(b)(2) Application, applicable DMF, and/or other corporate documents for Liquidia's Proposed Generic Product would infringe one or more claims of the '901 patent.

64. Upon information and belief, Liquidia will induce others to infringe one or more claims of the '901 patent under 35 U.S.C. § 271(b) by, among other things, actively and knowingly aiding and abetting others to infringe, including, but not limited to the manufacturer of Liquidia's Proposed Generic Product, or its API, or other subsequent purchasers, distributors, or users thereof, which product or its manufacture constitutes direct infringement of one or more claims of the '901 patent. Upon information and belief, Liquidia's aiding and abetting includes Liquidia's engagement of, contracting of, and/or encouragement of others to engage in the manufacture, use, sale, or importation of infringing products pursuant to Liquidia's 505(b)(2) Application.

65. Upon information and belief, Liquidia will also contributorily infringe one or more claims of the '901 patent under 35 U.S.C. § 271(c) in that Liquidia will make, use, sell, offer to sell, and/or import Liquidia's Proposed Generic Product and/or the API thereof, which Liquidia knows has no substantial non-infringing uses. Upon information and belief, subsequent purchasers, distributors, or users thereof will also directly infringe one or more claims of the '901 patent.

66. Upon information and belief, Liquidia will also infringe one or more claims of the '901 patent under 35 U.S.C. § 271(g) by importing, selling, offering to sell or using Liquidia's Proposed Generic Product or the API or an intermediate thereof which is neither materially changed by subsequent process nor a trivial or non-essential component of another product.

67. Upon information and belief, Liquidia was and is aware of the existence of the '901 patent and acted without a reasonable basis for believing that it would not be liable for infringement of the '901 patent, thus rendering this case "exceptional" under 35 U.S.C. § 285.

68. UTC will be substantially and irreparably damaged and harmed if Liquidia's infringement of the '901 patent is not enjoined by this Court. UTC does not have an adequate remedy at law.

COUNT 5: INFRINGEMENT OF THE '793 PATENT
UNDER 35 U.S.C. § 271(e)

69. UTC repeats and realleges each of the foregoing paragraphs as if fully set forth herein.

70. Upon information and belief, Liquidia's Proposed Generic Product is covered by one or more claims of the '793 patent.

71. Liquidia's maintenance of Liquidia's 505(b)(2) Application for the purpose of obtaining approval to engage in the commercial manufacture, use, sale, and/or offer for sale of Liquidia's Proposed Generic Product is an act of infringement of the '793 patent under 35 U.S.C. § 271(e)(2).

72. Upon information and belief, the commercial manufacture, use, offer for sale, sale and/or importation of Liquidia's Proposed Generic Product would infringe one or more claims of the '793 patent.

73. Upon information and belief, Liquidia was and is aware of the existence of the '793 patent and acted without a reasonable basis for believing that it would not be liable for infringement of the '793 patent, thus rendering this case "exceptional" under 35 U.S.C. § 285.

74. UTC will be substantially and irreparably damaged and harmed if Liquidia's infringement of the '793 patent is not enjoined by this Court. UTC does not have an adequate remedy at law.

COUNT 6: INFRINGEMENT OF THE '793 PATENT UNDER 35 U.S.C. §§ 271(a)-(c)

75. UTC repeats and realleges each of the foregoing paragraphs as if fully set forth herein.

76. Upon information and belief, upon FDA approval, Liquidia will manufacture, market, sell, offer to sell, import, and distribute Liquidia's Proposed Generic Product which will result in infringement of one or more claims of the '793 patent.

77. Liquidia's 505(b)(2) Application and Liquidia's intention to engage in the commercial manufacture, use, offer for sale, sale, and/or importation of Liquidia's Proposed Generic Product upon receiving FDA approval of Liquidia's 505(b)(2) Application prior to the expiration of the '793 patent creates an actual and justiciable controversy with respect to infringement of the '793 patent.

78. Upon information and belief, upon FDA's approval of Liquidia's 505(b)(2) Application, Liquidia's commercial manufacture, use, sale, offer for sale, and/or importation into the United States of Liquidia's Proposed Generic Product will directly infringe one or more claims of the '793 patent, and will indirectly infringe by actively inducing infringement by others, under 35 U.S.C. § 271(a), 35 U.S.C. § 271(b), and/or 35 U.S.C. § 271(c).

79. Upon information and belief, Liquidia's Proposed Generic Product or an intermediate in its manufacture as described in and/or directed by Liquidia's proposed labeling, Liquidia's 505(b)(2) Application, applicable DMF, and/or other corporate documents for Liquidia's Proposed Generic Product would infringe one or more claims of the '793 patent.

80. Upon information and belief, Liquidia will induce others to infringe one or more claims of the '793 patent under 35 U.S.C. § 271(b) by, among other things, actively and knowingly aiding and abetting others to infringe, including, but not limited to the manufacturer of Liquidia's Proposed Generic Product, or its API, or other subsequent purchasers, distributors, or users thereof, which product or its manufacture constitutes direct infringement of one or more claims of the '793 patent. Upon information and belief, Liquidia's aiding and abetting includes Liquidia's engagement of, contracting of, and/or encouragement of others to engage in the manufacture, use, sale, or importation of infringing products pursuant to Liquidia's 505(b)(2) Application.

81. Upon information and belief, Liquidia will also contributorily infringe one or more claims of the '793 patent under 35 U.S.C. § 271(c) in that Liquidia will make, use, sell, offer to sell, and/or import Liquidia's Proposed Generic Product and/or the API thereof, which Liquidia knows has no substantial non-infringing uses. Upon information and belief, subsequent purchasers, distributors, or users thereof will also directly infringe one or more claims of the '793 patent.

82. Upon information and belief, Liquidia was and is aware of the existence of the '793 patent and acted without a reasonable basis for believing that it would not be liable for infringement of the '793 patent, thus rendering this case "exceptional" under 35 U.S.C. § 285.

83. UTC will be substantially and irreparably damaged and harmed if Liquidia's infringement of the '793 patent is not enjoined by this Court. UTC does not have an adequate remedy at law.

PRAYER FOR RELIEF

WHEREFORE, UTC requests the following relief:

1. A judgment that:

   A. Liquidia has infringed the '066 patent, the '901 patent, and the '793 patent; and

   B. declaring that making, using, selling, offering for sale, or importing into the United States of Liquidia's Proposed Generic Product, or any product or compound that infringes one or more of the '066 patent, the '901 patent, and the '793 patent, prior to the expiration dates of the respective patents, will infringe, actively induce infringement of, and contribute to the infringement by others of the '066 patent, the '901 patent, and the '793 patent;

2. A judgment ordering that the effective date of any FDA approval of Liquidia's NDA No. 213005 permitting Liquidia to commercially manufacture, make, use, offer to sell, sell, market, or import into the United States Liquidia's Proposed Generic Product be not earlier than the latest of the expiration dates of the '066 patent, the '901 patent, and the '793 patent, inclusive of any extension(s) and additional period(s) of exclusivity to which UTC is or may become entitled;

3. A judgment pursuant to 35 U.S.C. § 271(e)(4)(B) preliminarily and permanently enjoining Liquidia, its officer, agents, servants, employees, parents, subsidiaries, affiliate

corporations, other business entities and all other persons acting in concert, participation, or privity with them, their successors, and assigns, from infringing, contributorily infringing, or inducing others to infringe the '066 patent, the '901 patent, and the '793 patent, including engaging in the commercial manufacture, use, sale, offer to sale and/or importation in the United States of the product that is the subject of Liquidia's 505(b)(2) Application and/or any applicable DMF until the expiration of the '066 patent, the '901 patent, and the '793 patent, inclusive of any extension(s) and additional period(s) of exclusivity to which UTC is or may become entitled;

4. A judgment awarding UTC damages or other monetary relief, pursuant to 35 U.S.C. §§ 271(e)(4)(c) and 284, if Liquidia engages in commercial manufacture, use, sale, offer to sell and/or importation into the United States of any product that is the subject of Liquidia's 505(b)(2) Application that infringes one or more claims of the '066 patent, the '901 patent, and the '793 patent;

5. A judgment declaring that, pursuant to 35 U.S.C. § 285, this is an exceptional case and awarding UTC its attorney's fees;

6. An award of costs and expenses in this action to UTC; and

7. Such further and other relief as this Court may deem just and proper.

MORRIS, NICHOLS, ARSHT & TUNNELL LLP

/s/ Jack B. Blumenfeld

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July 22, 2020

CERTIFICATE OF SERVICE

I hereby certify that on July 22, 2020, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on July 22, 2020, upon the following in the manner indicated:

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VIA ELECTRONIC MAIL

/s/ Jack B. Blumenfeld

Jack B. Blumenfeld (#1014)

EXHIBIT 2

FDA U.S. FOOD & DRUG ADMINISTRATION

NDA 213005

TENTATIVE APPROVAL

Liquidia Technologies, Inc.
Attention: Jennifer Weidman
VP Regulatory Affairs
419 Davis Dr., Suite 100
PO Box 110085
Research Triangle Park, NC 17709

Dear Ms. Weidman:

Please refer to your new drug application (NDA) dated and received January 24, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Yutrepia (treprostinil inhalation powder) Oral Inhalation.

We acknowledge receipt of your amendment dated May 7, 2021, which constituted a complete response to our November 24, 2020, action letter.

This NDA provides for the use of Yutrepia (treprostinil inhalation powder) Oral Inhalation for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability in patients with NYHA Functional Class II-III symptoms.

We have completed our review of this application, as amended. It is tentatively approved under 21 CFR 314.105 for use as recommended in the enclosed final labeling (Prescribing Information and Instructions for Use) submitted November 4, 2021, carton and container labeling submitted November 2, 2021. This determination is based upon information available to the Agency at this time, [i.e., information in your application and the status of current good manufacturing practices (cGMPs) of the facilities used in the manufacture and testing of the drug product]. This determination is subject to change on the basis of any new information that may come to our attention.

Final approval of your application is subject to expiration of a period of patent protection and/or exclusivity. Therefore, final approval of your application under section 505(c)(3) of the Act [21 U.S.C. 355(c)(3)] may not be granted before the period has expired.

A listed drug(s) upon which your application relies is subject to a period of patent protection and your application contains a certification(s) to one or more patents under section 505(b)(2)(A)(iv) of the FD&C Act stating that the patent(s) is/are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of, this drug product under this application ("paragraph IV certification").

Section 505(c)(3)(C) of the FD&C Act provides that approval of a new drug application submitted pursuant to section 505(b)(2) of the FD&C Act that includes a paragraph IV certification shall be made effective immediately, unless an action is brought for infringement of one or more of the patents that were the subject of a paragraph IV certification. If such a patent infringement action is brought prior to the expiration of 45 days from the later of the date the notice provided under section 505(b)(3) is received by the patent owner or approved application holder, your application is subject to a 30-month stay of approval, unless other conditions are met. You notified us that you complied with the requirements of section 505(b)(3) of the FD&C Act.

In addition, you have notified the Agency that the patent owner and/or approved application holder has initiated a patent infringement suit against you with respect to patents 9593066, 9604901, and 10716793 in the United States District Court for the District of Delaware, case number 1:20-cv-00755- RGA. Therefore, final approval cannot be granted until:

(1)
- expiration of the 30-month period provided for in section 505(c)(3)(C) beginning on the later of the date of receipt by any owner of the listed patent or application holder of the notice required under section 505(b)(3), unless the court has extended or reduced the period because of the failure of either party to reasonably cooperate in expediting the action, or
- the date the court decides that the patent(s) is/are invalid or not infringed as described in section 505(c)(3)(C)(i), (ii), (iii,) or (iv) of the FD&C Act, or,
- the listed patent(s) has/have expired, and

(2) we are assured there is no new information that would affect whether final approval should be granted.

To obtain final approval of this application, submit an amendment two or six months prior to the: (1) expiration of the patent(s) and/or exclusivity protection or (2) date you believe that your NDA will be eligible for final approval, as appropriate. In your cover letter, clearly identify your amendment as **"REQUEST FOR FINAL APPROVAL"**. This amendment should provide the legal/regulatory basis for your request for final approval and should include a copy of any relevant court order or judgment settlement, or licensing agreement, as appropriate. In addition to a safety update, the amendment should also identify changes, if any, in the conditions under which your product was tentatively approved, i.e., updated labeling; chemistry, manufacturing, and controls data; and risk evaluation and mitigation strategy (REMS). If there are no changes, clearly state so in your cover letter. Any changes require our review before final approval and the goal date for our review will be set accordingly.

Until we issue a final approval letter, this NDA is not approved.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We note that if this application is ultimately approved, you will need to meet these requirements.

PMR Descriptions:

- Phase 3 randomized, double-blind, placebo-controlled trial to evaluate the efficacy, safety, and pharmacokinetics of LIQ861 (**T**reprostinil) in children with WHO Group 1 Pulmonary Arterial Hypertension, aged 7 to 17 years; 16-week trial.

- Phase 3 PK and safety study in PH, open-label, dose escalation study to assess safety, tolerability, and pharmacokinetics of LIQ861 in children with WHO Group 1 Pulmonary Arterial Hypertension, aged 3 to 6 years; 12-week trial.

If you have any questions, please call Maryam Changi, Regulatory Project Manager, at (240) 402-2725.

Sincerely,

{See appended electronic signature page}

Norman Stockbridge, MD, PhD
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE(S):
- Content of Labeling
  - Prescribing Information
  - Instructions for Use
- Carton and Container Labeling

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use YUTREPIA™ safely and effectively. See full prescribing information for YUTREPIA™.

YUTREPIA™ (treprostinil) inhalation powder, for oral inhalation
Initial U.S. Approval: 2002

----------INDICATIONS AND USAGE----------
YUTREPIA is a prostacyclin mimetic indicated for the treatment of pulmonary arterial hypertension (PAH; WHO Group 1) to improve exercise ability in patients with NYHA Functional Class II-III symptoms. (1)

----------DOSAGE AND ADMINISTRATION----------
- For oral inhalation only. Do not swallow YUTREPIA capsules. Use only with the provided inhaler (2)
- YUTREPIA should be administered 3 to 5 times per day. The contents of each capsule can be inhaled in 2 breaths. (2.1)
- See *Dosage and Administration* for full instructions on dosing of patients who are treprostinil-naïve or transitioning from treprostinil inhalation solution to YUTREPIA (2.1)

----------DOSAGE FORMS AND STRENGTHS----------
YUTREPIA inhalation powder contained in capsule is available in 4 strengths: 26.5 mcg, 53 mcg, 79.5 mcg, 106 mcg (3)

----------CONTRAINDICATIONS----------
None (4)

----------WARNINGS AND PRECAUTIONS----------
- Treprostinil may cause symptomatic hypotension. (5.1)
- Treprostinil inhibits platelet aggregation and increases the risk of bleeding. (5.2)
- Dosage adjustments may be necessary if inhibitors or inducers of CYP2C8 are added or withdrawn. (5.3, 7.1)

----------ADVERSE REACTIONS----------
Most common adverse reactions with YUTREPIA (≥10%) are cough, headache, throat irritation, and dizziness. (6)

To report SUSPECTED ADVERSE REACTIONS, contact Liquidia Technologies, Inc. at 1-XXX-XXX-XXXX or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling (Instructions for Use).

Revised: 11/2021

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

YUTREPIA™ is indicated for the treatment of pulmonary arterial hypertension (PAH) (WHO Group 1) to improve exercise ability in patients with NYHA Functional Class II-III symptoms.

2 DOSAGE AND ADMINISTRATION

2.1 Usual Dosage In Adults

YUTREPIA capsules are for oral inhalation only and should be used only with the supplied inhaler.

YUTREPIA Dosing in treprostinil-naïve patients:

In patients naïve to treprostinil, therapy should begin with 26.5 mcg 3 to 5 times per day, in 2 breaths based on patient response.

Dosing in patients transitioning from treprostinil inhalation solution (Tyvaso):

Patients transitioning from treprostinil inhalation solution (Tyvaso), can begin YUTREPIA therapy 3 to 5 times per day, in 2 breaths, using the doses specified below (Table 1):

Table 1: YUTREPIA Dosing in Patients Transitioning from Treprostinil Inhalation Solution

Current Tyvaso Dose*	YUTREPIA Dose
Breaths	mcg
≤5	26.5
≥6 and ≤8	53
≥9 and ≤11	79.5
≥12 and ≤14	106
≥15 and ≤17	132.5
≥18	159

*Each breath of Tyvaso delivers approximately 6 mcg of treprostinil

In treprostinil-naïve patients and those transitioning from treprostinil inhalation solution, dose increases of 26.5 mcg per dose each week may be implemented, as tolerated. The target maintenance dosage is 79.5-106 mcg, 4 times daily. Doses above 848 mcg per day have not been studied.

3 DOSAGE FORMS AND STRENGTHS

YUTREPIA inhalation powder contained in capsule available in 4 strengths:

- 26.5 mcg: opaque yellow cap and clear body capsule with "LIQUIDIA 26.5" in black radial imprint on capsule cap.
- 53 mcg: opaque green cap and clear body capsule with "LIQUIDIA 53" in white radial imprint on capsule cap.

- 79.5 mcg: opaque blue cap and clear body capsule with "LIQUIDIA 79.5" in white radial imprint on capsule cap.
- 106 mcg: opaque purple cap and clear body capsule with "LIQUIDIA 106" in white radial imprint on capsule cap.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Risk of Symptomatic Hypotension

Treprostinil is a pulmonary and systemic vasodilator. In patients with low systemic arterial pressure, treatment with treprostinil may produce symptomatic hypotension.

5.2 Risk of Bleeding

Treprostinil inhibits platelet aggregation and increases the risk of bleeding.

5.3 Effect of Other Drugs on Treprostinil

Co-administration of a cytochrome P450 (CYP) 2C8 enzyme inhibitor (e.g., gemfibrozil) may increase exposure (both C_{max} and AUC) to treprostinil. Co-administration of a CYP2C8 enzyme inducer (e.g., rifampin) may decrease exposure to treprostinil. Increased exposure is likely to increase adverse events associated with treprostinil administration, whereas decreased exposure is likely to reduce clinical effectiveness *[see Drug Interactions (7.1) and Clinical Pharmacology (12.3)]*.

6 ADVERSE REACTIONS

The following potential adverse reactions are described in Warnings and Precautions (5):

- Decrease in systemic blood pressure *[see Warnings and Precautions (5.1)]*.
- Bleeding *[see Warnings and Precautions (5.2)]*.

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

The safety and tolerability of YUTREPIA was evaluated in an open label study (INSPIRE) of 121 patients with PAH (WHO Group 1 and NYHA Functional Class II [80 patients] and Class III [41 patients]) followed for up to 2 months. The most commonly reported adverse reactions included cough, headache, throat irritation, dizziness, which are known side effects of treprostinil inhalation solution. Table 2 lists the adverse reactions that occurred at a rate of at least 4% of the overall INSPIRE safety population. The adverse reactions in the INSPIRE study were consistent with those observed in previous studies of inhaled treprostinil.

Table 2: Adverse Reactions Occurring in ≥ 4% of Patients in the INSPIRE Study

	Transition* N=55	Add-On† N=66
Adverse Reaction	**n (%)**	**n (%)**
Cough	15 (27)	36 (55)
Headache	14 (25)	18 (27)
Throat Irritation	5 (9)	14 (21)
Dizziness	6 (11)	7 (11)
Diarrhea	3 (6)	8 (12)
Chest Discomfort	5 (9)	5 (8)
Nausea	4 (7)	5 (8)
Dyspnea	3 (6)	3 (5)
Flushing	1 (2)	5 (8)
Oropharyngeal Pain	1 (2)	4 (6)

*Transition: Patients were on stable doses of treprostinil inhalation solution for at least 3 months prior to enrollment in the study and transitioned to treatment with YUTREPIA.

†Add-on: Patients were prostacyclin-naïve and were taking no more than 2 approved oral PAH therapies for at least 3 months at time of enrollment and addition of treatment with YUTREPIA.

6.2 Adverse Reactions Identified in Post-Marketing Experience

The following adverse reaction has been identified during the post-approval use of treprostinil inhalation solution. Because this reaction is reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure:

- Angioedema

7 DRUG INTERACTIONS

7.1 Effect of Cytochrome P450 Inhibitors and Inducers

In vitro studies of human hepatic microsomes showed that treprostinil does not inhibit cytochrome P450 (CYP) isoenzymes CYP1A2, CYP2A6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1 and CYP3A.

Additionally, treprostinil does not induce cytochrome P450 isoenzymes CYP1A2, CYP2B6, CYP2C9, CYP2C19, and CYP3A.

Human pharmacokinetic studies with an oral formulation of treprostinil (treprostinil diolamine) indicated that co-administration of the cytochrome P450 (CYP) 2C8 enzyme inhibitor gemfibrozil increases exposure (both C_{max} and AUC) to treprostinil. Co-administration of the CYP2C8 enzyme inducer rifampin decreases exposure to treprostinil. It is unclear if the safety and efficacy of treprostinil by the inhalation route are altered by inhibitors or inducers of CYP2C8 *[see Warnings and Precautions (5.3)]*.

7.2 Effect of Other Drugs on Treprostinil

Drug interaction studies have been carried out with treprostinil (oral or subcutaneous) co-administered with acetaminophen (4 g/day), warfarin (25 mg/day), and fluconazole (200 mg/day), respectively, in healthy volunteers. These studies did not show a clinically significant effect on the pharmacokinetics of treprostinil. Treprostinil does not affect the pharmacokinetics or pharmacodynamics of warfarin. The pharmacokinetics of R- and S- warfarin and the INR in healthy subjects given a single 25 mg dose of warfarin were unaffected by continuous subcutaneous infusion of treprostinil at an infusion rate of 10 ng/kg/min.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Limited case reports of treprostinil use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. However, there are risks to the mother and the fetus associated with pulmonary arterial hypertension (see *Clinical Considerations*). In animal studies, no adverse reproductive and developmental effects were seen for treprostinil at ≥9 and ≥145 times the human exposure when based on C_{max} and AUC, respectively, following a single YUTREPIA dose of 79.5 mcg *[see Clinical Pharmacology (12.3)]*.

The estimated background risk of major birth defects and miscarriage for the indicated populations is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2 to 4% and 15 to 20%, respectively.

Clinical Considerations

Disease-associated maternal and embryo-fetal risk

Pulmonary arterial hypertension is associated with an increased risk of maternal and fetal mortality.

Data

Animal reproduction studies have been conducted with treprostinil via continuous subcutaneous administration and with treprostinil diolamine administered orally. In studies with orally administered treprostinil diolamine, no adverse effect doses for fetal viability/growth, fetal development (teratogenicity), and postnatal development were determined in rats. In pregnant rats, no evidence of harm to the fetus was observed following oral administration of treprostinil diolamine at the highest dose tested (20 mg/kg/day), which represents about 154 and 1479 times the human exposure, when based on C_{max} and AUC, respectively, following a single YUTREPIA dose of 79.5 mcg. In pregnant rabbits, external fetal and soft tissue malformations and fetal skeletal malformation occurred. The dose at which no adverse effects were seen (0.5 mg/kg/day) represents about 9 and 145 times the human exposure, when based on C_{max} and AUC, respectively, following a single YUTREPIA dose of 79.5 mcg. No treprostinil treatment-related effects on labor and delivery were seen in animal studies. Animal reproduction studies are not always predictive of human response.

8.2 Lactation

Risk Summary

There are no data on the presence of treprostinil in human milk, the effects on the breastfed infant, or the effects on milk production.

8.4 Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use

Placebo-controlled clinical studies of treprostinil inhalation solution did not include sufficient numbers of patients aged 65 years and over to determine whether they respond differently from younger patients. The open-label INSPIRE study in PAH patients included 28 patients aged 65 and over in which no age-related differences were noted. In general, dose selection for an elderly patient should be cautious, reflecting the greater frequency of hepatic, renal, or cardiac dysfunction, and of concomitant diseases or other drug therapy.

8.6 Patients with Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects with mild-to-moderate hepatic insufficiency. Uptitrate slowly when treating patients with hepatic insufficiency because of the risk of an increase in systemic exposure which may lead to an increase in dose-dependent adverse effects. Treprostinil has not been studied in patients with severe hepatic insufficiency *[see Clinical Pharmacology (12.3)]*.

8.7 Patients with Renal Insufficiency

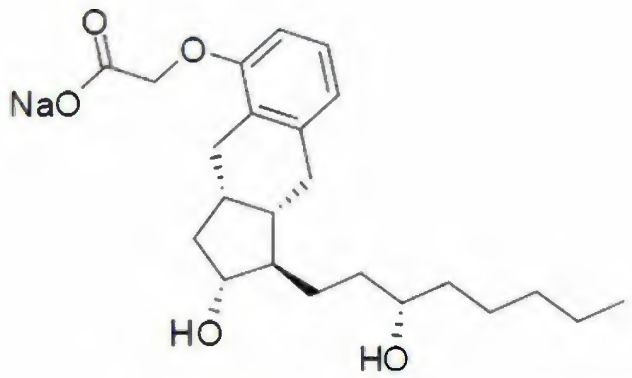
No dose adjustments are required in patients with renal impairment. Treprostinil is not cleared by dialysis *[see Clinical Pharmacology (12.3)]*.

10 OVERDOSAGE

In general, symptoms of overdose with treprostinil include flushing, headache, hypotension, nausea, vomiting, and diarrhea. Provide general supportive care until the symptoms of overdose have resolved.

11 DESCRIPTION

YUTREPIA contains treprostinil sodium, a prostacyclin vasodilator. The chemical name for tresprostinil sodium is 2-{[(1R,2R,3aS,9aS)-2-hydroxy-1-[(3S)-3-hydroxyoctyl]-1H,2H,3H,3aH,4H,9H,9aH-cyclopenta[b]naphthalen-5-yl]oxy}acetic acid, sodium salt with the structural formula:



Treprostinil sodium has a molecular formula of $C_{23}H_{33}O_5Na$ and a molecular weight of 412.49 daltons equivalent to 390.5 daltons of Treprostinil

YUTREPIA inhalation powder contained in a capsule is intended for oral inhalation. The capsule contains white to off-white powder of treprostinil sodium and the inactive ingredients trehalose, polysorbate 80, L-leucine, sodium citrate, and sodium chloride. 26.5 mcg of treprostinil is equivalent to 28 mcg of treprostinil sodium.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

The major pharmacologic actions of treprostinil are direct vasodilation of pulmonary and systemic arterial vascular beds and inhibition of platelet aggregation.

12.2 Pharmacodynamics

In animals, the vasodilatory effects reduce right and left ventricular afterload and increase cardiac output and stroke volume. Other studies have shown that treprostinil causes a dose-related negative inotropic and lusitropic effect. No major effects on cardiac conduction have been observed. Treprostinil produces vasodilation and tachycardia.

Cardiac Electrophysiology

In a clinical trial of 240 healthy volunteers, single doses of treprostinil inhalation solution 54 mcg (the target maintenance dose per session) and 84 mcg (supratherapeutic inhalation dose) prolonged the corrected QTc interval by approximately 10 ms. The QTc effect dissipated rapidly as the concentration of treprostinil decreased.

12.3 Pharmacokinetics

Absorption

in healthy volunteer studies, the systemic exposure (AUC and C_{max}) post-inhalation was shown to be proportional to the YUTREPIA doses administered (25 mcg – 150 mcg). The treprostinil mean C_{max}, mean AUC_{inf} and median T_{max} following a single inhaled target maintenance dose of 79.5 mcg YUTREPIA were 1.48 ng/mL, 1.04 hr.ng/mL and 0.13 hr, respectively.

Distribution

In vitro treprostinil is 91% bound to human plasma proteins over the 330-10,000 ng/mL concentration range.

Metabolism and Excretion

Of subcutaneously administered treprostinil, only 4% is excreted unchanged in urine. Treprostinil is substantially metabolized by the liver, primarily by CYP2C8. Metabolites are excreted in urine (79%) and feces (13%) over 10 days. Five apparently inactive metabolites were detected in the urine, each accounting for 10-15% of the dose administered. Four of the metabolites are products of oxidation of the 3-hydroxyloctyl side chain and one is a glucuroconjugated derivative (treprostinil glucuronide).

Elimination

Following inhaled administration of YUTREPIA, disposition and elimination is monophasic with a half-life of approximately 30 minutes.

Specific Populations

Hepatic Insufficiency

Plasma clearance of treprostinil, delivered subcutaneously, was reduced up to 80% in subjects presenting with mild-to-moderate hepatic insufficiency. Treprostinil has not been studied in patients with severe hepatic insufficiency *[see Use in Specific Populations (8.6)]*.

Renal Insufficiency

In patients with severe renal impairment requiring dialysis (n=8), administration of a single 1 mg dose of orally administered treprostinil pre-and post-dialysis resulted in AUC0-inf that was not significantly altered compared to healthy subjects *[see Use in Specific Populations (8.7)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

A two-year rat carcinogenicity study was performed with treprostinil inhalation solution at target treprostinil doses of 5.26, 10.6, and 34.1 µg/kg/day. There was no evidence for carcinogenic potential associated with treprostinil inhalation in rats at systemic exposure levels up to 35 times following a single YUTREPIA dose of 79.5 mcg *[see Clinical Pharmacology (12.3)]*. *In vitro* and *in vivo* genetic toxicology studies did not demonstrate any mutagenic or clastogenic effects of treprostinil. Treprostinil sodium did not affect fertility or mating performance of male or female rats given continuous subcutaneous (sc) infusions at rates of up to 450 ng treprostinil/kg/min. In this study, males were dosed from 10 weeks prior to mating and through the 2-week mating period. Females were dosed from 2 weeks prior to mating until gestational day 6.

Oral administration of treprostinil diolamine to Tg.rasH2 mice at 0, 5, 10 and 20 mg/kg/day in males and 0, 3, 7.5 and 15 mg/kg/day in females daily for 26 weeks did not significantly increase the incidence of tumors.

Treprostinil diolamine was tested *in vivo* in a rat micronucleus assay and did not induce an increased incidence of micronucleated polychromatic erythrocytes.

13.2 Animal Toxicology and/or Pharmacology

In a 2-year rat study with treprostinil inhalation at target doses of 5.26, 10.6, and 34.1 mcg/kg/day, there were more deaths (11) in the mid- and high-dose treprostinil groups during the first 9 weeks of the study, compared to 1 in control groups. At the high-dose level, males showed a higher incidence of inflammation in teeth and preputial gland, and females showed high incidences of inflammation and urothelial hyperplasia in the urinary bladder. The exposures in rats at mid- and high-dose levels were about 15 and 35 times, respectively, the clinical exposure following a single YUTREPIA dose of 79.5 mcg *[see Clinical Pharmacology (12.3)]*.

14 CLINICAL STUDIES

14.1 Pulmonary Arterial Hypertension (WHO Group 1)

TRIUMPH I was a 12-week, randomized, double-blind, placebo-controlled multi-center study of patients with PAH. The study population included 235 clinically stable patients with pulmonary arterial hypertension (WHO Group 1), nearly all with NYHA Class III (98%) symptoms who were receiving either bosentan (an endothelin receptor antagonist) or sildenafil (a phosphodiesterase-5 inhibitor) for at least three months prior to study initiation. Concomitant therapy also could have included anticoagulants, other vasodilators (e.g., calcium channel blockers), diuretics, oxygen, and digitalis, but not a prostacyclin. These patients were administered either placebo or treprostinil inhalation solution in four daily treatment sessions with a target dose of 9 breaths (equivalent to 79.5 mcg YUTREPIA) per session over the course of the 12-week study. Patients were predominantly female (82%), had the origin of PAH as idiopathic/heritable (56%), secondary to connective tissue diseases (33%) or secondary to HIV or previous use of anorexigens (12%); bosentan was the concomitant oral medication in 70% of those enrolled, sildenafil in 30%.

The primary efficacy endpoint of the trial was the change in six-minute walk distance (6MWD) relative to baseline at 12 weeks. 6MWD was measured at peak exposure (between 10 and 60 minutes after dosing), and 3-5 hours after bosentan or 0.5-2 hours after sildenafil. Patients receiving treprostinil inhalation solution had a placebo-corrected median change from baseline in peak 6MWD of 20 meters at Week 12 ($p<0.001$).

The distribution of these 6MWD changes from baseline at Week 12 were plotted across the range of observed values (Figure 1). 6MWD measured at trough exposure (defined as measurement of 6MWD at least 4 hours after dosing) improved by 14 meters. There were no placebo-controlled 6MWD assessments made after 12 weeks.

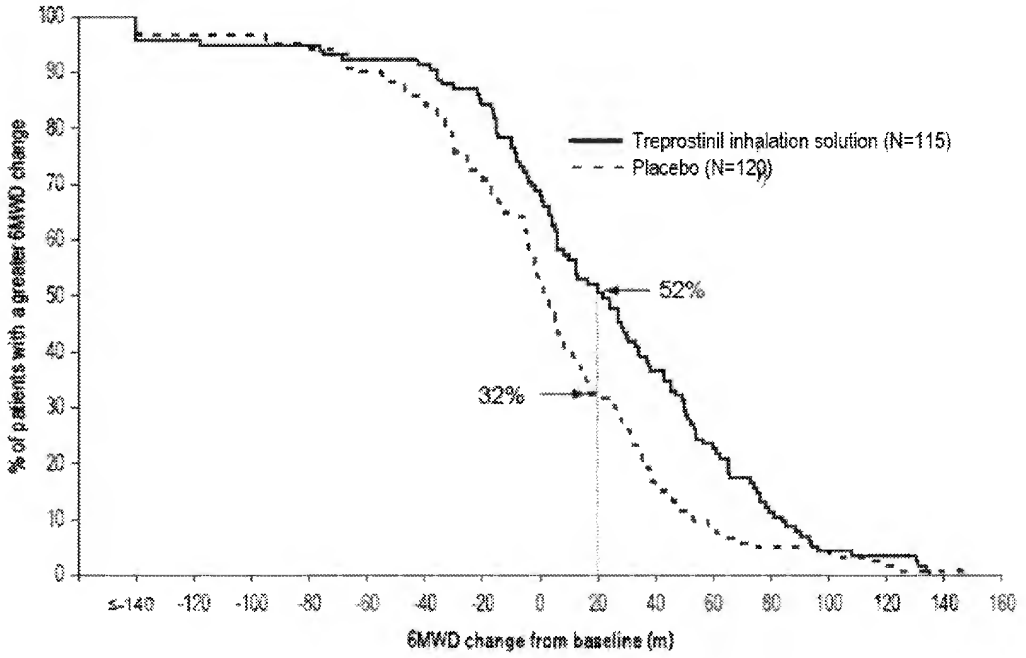


Figure 1. Distributions of 6MWD Changes from Baseline at Week 12 during Peak Plasma Concentration of Treprostinil Inhalation Solution

The placebo-corrected median treatment effect on 6MWD was estimated (using the Hodges-Lehmann estimator) within various subpopulations defined by age quartile, gender, geographic region of the study site, disease etiology, baseline 6MWD quartile, and type of background therapy (Figure 2).

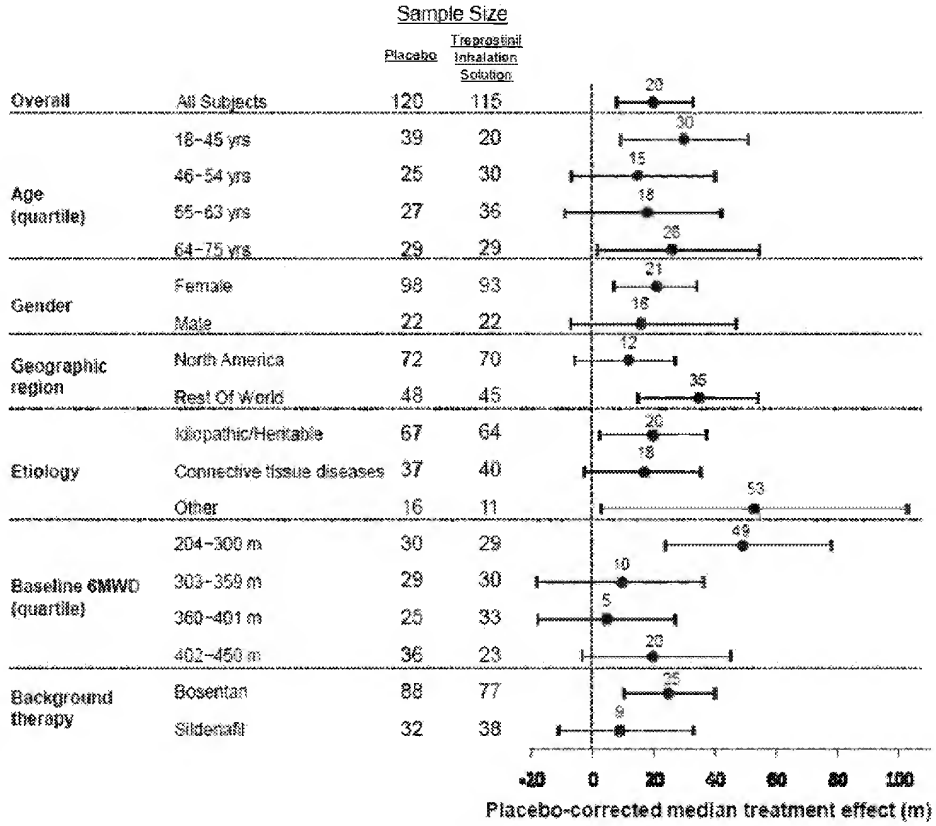


Figure 2. Placebo-Corrected Median Treatment Effect (Hodges-Lehmann estimate with 95% CI) on 6MWD Change from Baseline at Week 12 During Peak Plasma Concentration of Treprostinil Inhalation Solution for Various Subgroups

16 HOW SUPPLIED/STORAGE AND HANDLING

YUTREPIA is supplied in a carton consisting of 1 capsule based, dry powder inhaler (referred to as "inhaler"), 28 capsules (7 foil blister cards of 4 capsules each), and 7 single-use cleaning brushes. The individual capsule well is connected by an air channel to a separate blister well containing a desiccant strip. Descriptions of YUTREPIA carton by capsule strength are provided in Table 3 below:

Table 3: YUTREPIA Carton Contents by Capsule Strength

Capsule Strength (mcg treprostinil)	Capsule Description	NDC Number
26.5	Opaque yellow cap, clear body, imprinted with "LIQUIDIA 26.5" in black ink radially on cap	72964-011-01
53	Opaque green cap, clear body, imprinted with "LIQUIDIA 53" in white ink radially on cap	72964-012-01
79.5	Opaque blue cap, clear body, imprinted with "LIQUIDIA 79.5" in white ink radially on cap	72964-013-01
106	Opaque purple cap, clear body, imprinted with "LIQUIDIA 106" in white ink radially on cap	72964-014-01

YUTREPIA inhalation powder capsules should only be delivered using the capsule-based inhaler.. The off-white plastic inhaler consists of a blue protective cap marked with YUTREPIA and a base with a mouthpiece, capsule chamber, and two blue push buttons. Discard the inhaler device after 7 days of use or 56 actuations, whichever comes first.

Store at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F) [see USP Controlled Room Temperature].

Capsules should remain in the blister to protect them from moisture and light, and each capsule should be removed only when ready to administer a dose.

Keep out of the reach of children.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Instructions for Use).

Train patients in the administration process for YUTREPIA, including dosing, inhaler preparation, administration, cleaning, and maintenance, according to the instructions for use *[see Instructions for Use]*.

To avoid potential interruptions in drug delivery because of equipment malfunction, patients should have access to a back-up.

In the event that a scheduled dose is missed, take another dose as soon as possible.

Distributed by: Liquidia Technologies, Inc. Morrisville, NC 27560

Instructions for Use
YUTREPIA™ (you-TREP-ee-uh)
(trepostinil)
inhalation powder, for oral inhalation

This Instructions for Use contains information on how to inhale YUTREPIA™. Read these Instructions for Use before you start using YUTREPIA and each time you get a refill. There may be new information. This information does not take the place of talking to your healthcare provider about your medical condition or treatment.

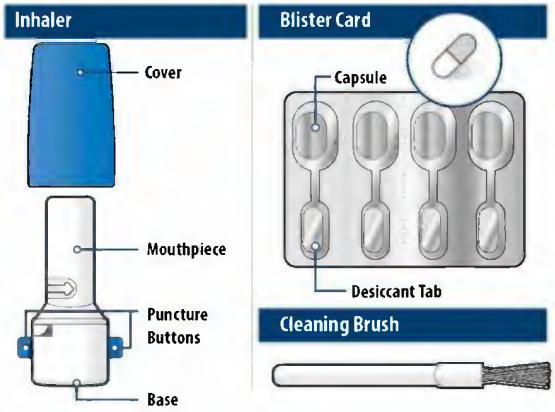
Your healthcare provider should show you or your caregiver how to use YUTREPIA the right way before you use it for the first time.

Important information you need to know before inhaling YUTREPIA inhalation powder:

- **Do not** swallow YUTREPIA capsules. YUTREPIA is for inhalation only.
- Use YUTREPIA as prescribed by your healthcare provider.
- YUTREPIA capsules come in 4 strengths: 26.5 mcg, 53 mcg, 79.5 mcg, and 106 mcg.
- If your prescribed dose is more than 106 mcg, you will need to inhale 2 YUTREPIA capsules. **See Figure C**: Dosing Chart to help you identify the 2 capsules needed for your prescribed dose. Only use the capsule combinations in the Dosing Chart when your prescribed dose is more than 106 mcg.
- **The capsule must be inhaled within 5 minutes of opening the blister card or the full dose may not be administered. Read through this instruction sheet prior to the first use of this product.**
- Always inhale each capsule 2 times to make sure you get your full dose of YUTREPIA.
- **Do not** wash the inhaler. Keep the inhaler dry.
- Wash and dry your hands your hands before using YUTREPIA.
- If the contents of the capsule comes in contact with your skin or eyes, rinse the area immediately with water.
- YUTREPIA capsules should remain in the blister card(s) and each capsule should be removed only when ready to deliver a dose.

Storing YUTREPIA

- Store YUTREPIA carton in a clean, dry place at room temperature between 68°F to 77°F (20°C to 25°C).
- Leave YUTREPIA capsules in blister card to protect from moisture and light.
- Throw away the inhaler after 7 days of use or 56 capsules whichever comes first.
- **Keep YUTREPIA and all medicines out of the reach of children.**

Text	Illustration
Get to know YUTREPIA	
The YUTREPIA carton contains (See Figure A): • 1 dry powder inhaler (called "inhaler" in these instructions) • 7 Foil blister cards of YUTREPIA capsules (called "capsules" in these instructions) containing 4 capsules each, in one of 4 available strengths • 7 Cleaning brushes (1 for each day) • 1 Desiccant tab within each blister strip to keep the capsule dry and prevent moisture. Throw away the blister strip and the desiccant tab after removing the capsule.	 **Figure A**

Preparing to use YUTREPIA

The capsule must be inhaled within 5 minutes of opening the blister card. Ensure all supplies are gathered and you are familiar with the use of the product prior to opening the card.

STEP 1. Gather your supplies.

a. Place your YUTREPIA carton on a clean, dry surface.
b. Remove the inhaler and foil blister cards from the carton **(See Figure B)**.

Figure B

STEP 2. Select the capsule(s) for your dose.

Use the Dosing Chart **(See Figure C)** to help you identify the capsule(s) needed for your prescribed dose.

- If your prescribed dose is more than 106 mcg, you will need to inhale 2 capsules per the table above.
- Only load and inhale 1 capsule at a time.
- All capsules in a carton are the same strength. If your prescribed dose requires 2 capsules of different strengths, you will need to select your capsules from 2 separate cartons.

IMPORTANT: For doses requiring 2 capsules, only use the capsule combinations presented in the Dosing Chart above **(See Figure C)**. The order for inhaling 2 capsules does not matter, regardless of capsule strength.

		Capsules Needed
Dose (mcg)	26.5	1 Yellow (26.5 mcg)
	53	1 Green (53 mcg)
	79.5	1 Blue (79.5 mcg)
	106	1 Purple (106 mcg)
	132.5	1 Green (53 mcg) + 1 Blue (79.5 mcg)
	159	2 Blue (79.5 mcg)
	185.5	1 Blue (79.5 mcg) + 1 Purple (106 mcg)
	212	2 Purple (106 mcg)

Figure C

STEP 3. Check the inhaler and blister card(s).

a. Look at the inhaler and blister card(s) to make sure they are not damaged **(See Figure D)**.
Do not use the inhaler or capsules if they are damaged.

b. Look at the expiration date on the blister cards to make sure it has not passed **(See Figure E).**
Do not use the capsules if the expiration date has passed.

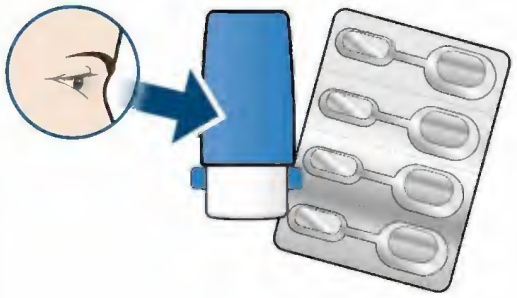


Figure D

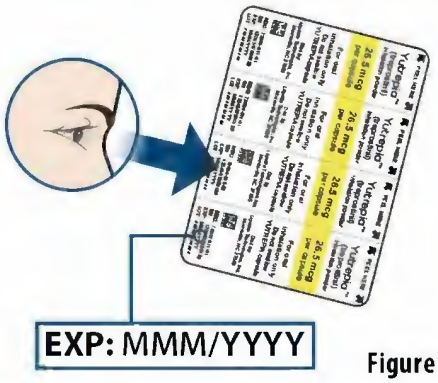


Figure E

Loading YUTREPIA

STEP 4. Open the inhaler.

a. Pull the cover straight off the inhaler **(See Figure F).**

Figure F

b. Rotate the mouthpiece in the direction of the arrow (counter-clockwise) to open the inhaler and expose the capsule chamber **(See Figure G)**.
If the mouthpiece separates from the base of the inhaler, gently reattach the 2 pieces and continue to follow the instructions.

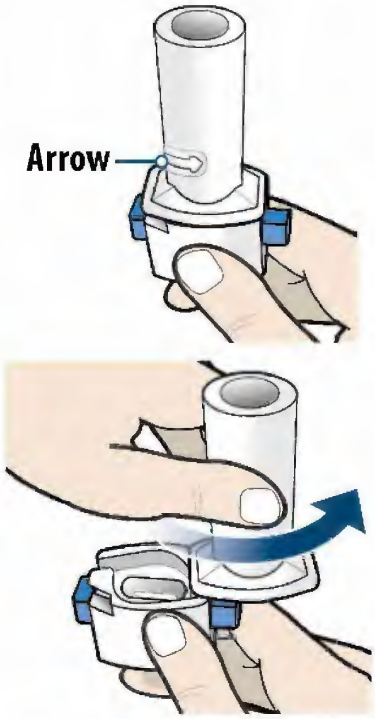


Figure G

STEP 5. Remove the capsule from the blister strip.

a. Separate 1 blister strip by tearing at the pre-cut lines **(See Figure H)**.
Do not remove a capsule from the blister strip until you are ready to deliver your dose.

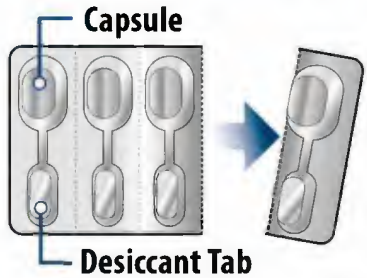


Figure H

b. Peel the foil away from the blister strip, remove the capsule **(See Figure I)**.

Do not swallow the capsule.
Do not push the capsule through the foil.
Do not remove the desiccant tab.
Capsule must be used **within 5 minutes** of opening the blister card.

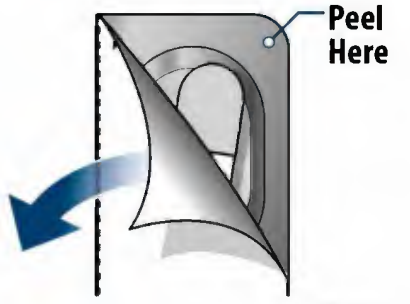


Figure I

STEP 6. Secure the capsule in the inhaler.

a. Hold the inhaler in an upright position.
b. Place the capsule in the capsule chamber in the base of the inhaler **(See Figure J)**. Only load 1 capsule.
Do not place a capsule in the mouthpiece.
Do not swallow capsules.

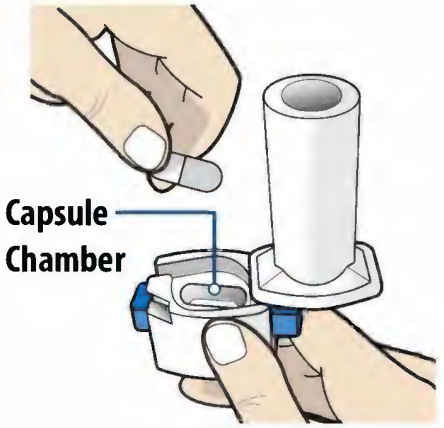


Figure J

STEP 7. Puncture the capsule.

a. Put one finger on top of the capsule to hold it down **(See Figure K)**.
b. While still holding down the capsule, firmly press both puncture buttons all the way in with your other hand **(See Figure L)**.
Then let go of (release) the puncture buttons.
This will puncture the capsule.
You only need to press the puncture buttons 1 time.
c. Hold the base of the inhaler and rotate the mouthpiece to close it.

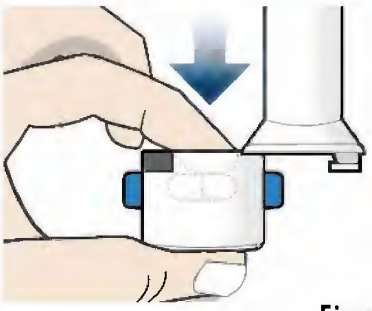


Figure K

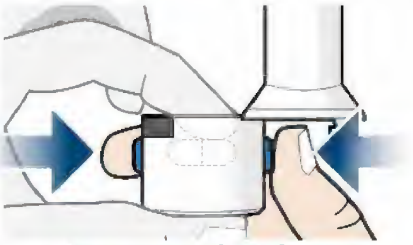


Figure L

Inhaling YUTREPIA

STEP 8. Position the inhaler.
Hold the inhaler upright and away from your mouth. **(See Figure M)**.
Do not hold the inhaler by the puncture buttons.

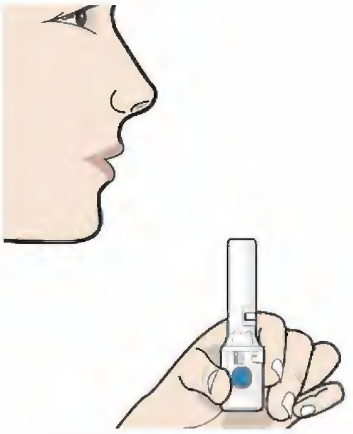


Figure M

STEP 9. Breathe out (exhale).
Breathe out fully and away from the inhaler **(See Figure N)**.
Do not exhale into the mouthpiece.

Figure N

STEP 10. Breathe in deeply (inhale)

a. Close your lips around the mouthpiece **(See Figure O)**.
b. Tilt your head back slightly **(See Figure O)**.
c. Take a comfortable deep breath in (inhale) until your lungs feel full **(See Figure O)**.
As you inhale, you will hear or feel a whirring noise as the capsule spins and releases medicine.

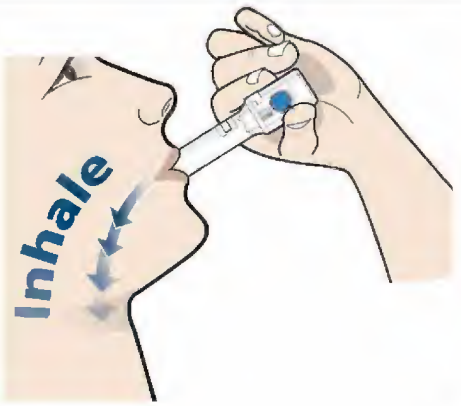


Figure O

STEP 11. Hold breath, then breathe out (exhale). a. Take the inhaler out of your mouth and hold your breath for 5 seconds or as long as you comfortably can **(See Figure P)**. b. Then breathe out normally. **IMPORTANT:** If you cough when inhaling, repeat STEP 8 through11.	 **Figure P**
STEP 12. Inhale again. To make sure the capsule is completely emptied of medicine, repeat STEP 8 through11 **(See Figure Q)**. Always inhale each capsule 2 times to make sure you get your full dose.	 **Figure Q**

Removing and disposing of the capsule

STEP 13. Open the inhaler.

a. Rotate the mouthpiece in the direction of the arrow (counter-clockwise) to open the inhaler and expose the capsule chamber **(See Figure R)**.
b. Remove the used (empty) capsule and throw away (dispose of) into household trash **(See Figure S)**.
c. See box below if you need to use more than 1 capsule to complete your prescribed dose.
d. Continue to Step 14 if you have completed your prescribed dose.

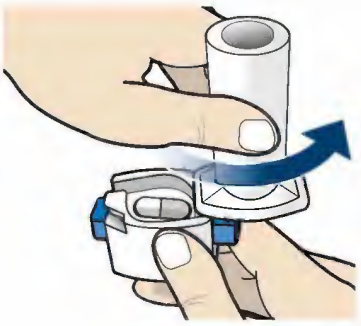


Figure R

Figure S

When dosing with more than one capsule (for doses 132.5 mcg and larger)

If you need to use more than one capsule to complete your prescribed dose, repeat STEP 4 through 13 with each additional capsule.

The order for dosing the capsules does not matter, regardless of capsule strength.

Closing and storing the inhaler

STEP 14. Close the inhaler.

a. Hold the base of the inhaler and rotate the mouthpiece to close it **(See Figure T).**
b. Put the cover on the inhaler **(See Figure U)**.
c. Store the inhaler in a clean, dry place at room temperature.

Figure T

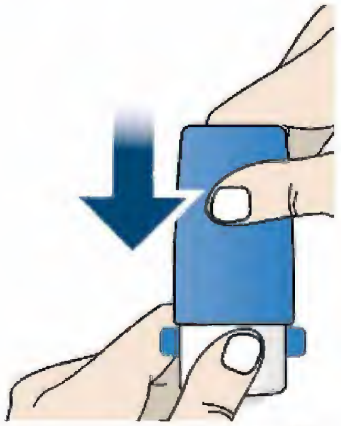


Figure U

Cleaning the inhaler (at end of each day)

Clean the outside and inside of the inhaler after your last dose of the day.

a. Wipe the mouthpiece with a dry paper towel, tissue, or clean dry cloth **(See Figure V)**.

b. Use the cleaning brush provided to clean the capsule chamber in order to remove visible powder buildup **(See Figure W)**.
NOTE: Throw away the brush after cleaning. Use only 1 brush each day.

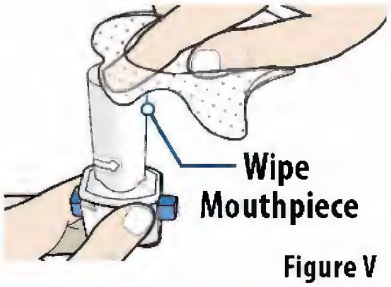


Figure V

Figure W

Disposing of the inhaler

Throw away (dispose of) the inhaler into household trash after 7 days of use.

The inhaler is reusable and will last for 7 days (1 week) or 56 capsules, whichever comes first.
(See Figure X).

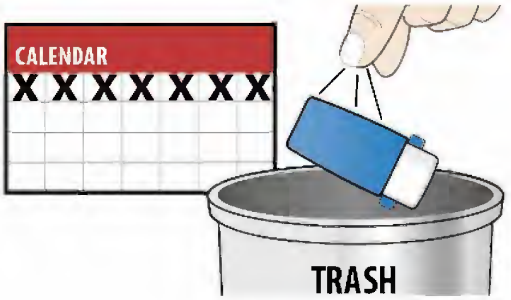


Figure X

Distributed by: Liquidia Technologies, Inc. Morrisville, NC 27560
For more information call 1-800-###-#### or go to www.YUTREPIA.com

This Instructions for Use has been approved by the U.S. Food and Drug Administration

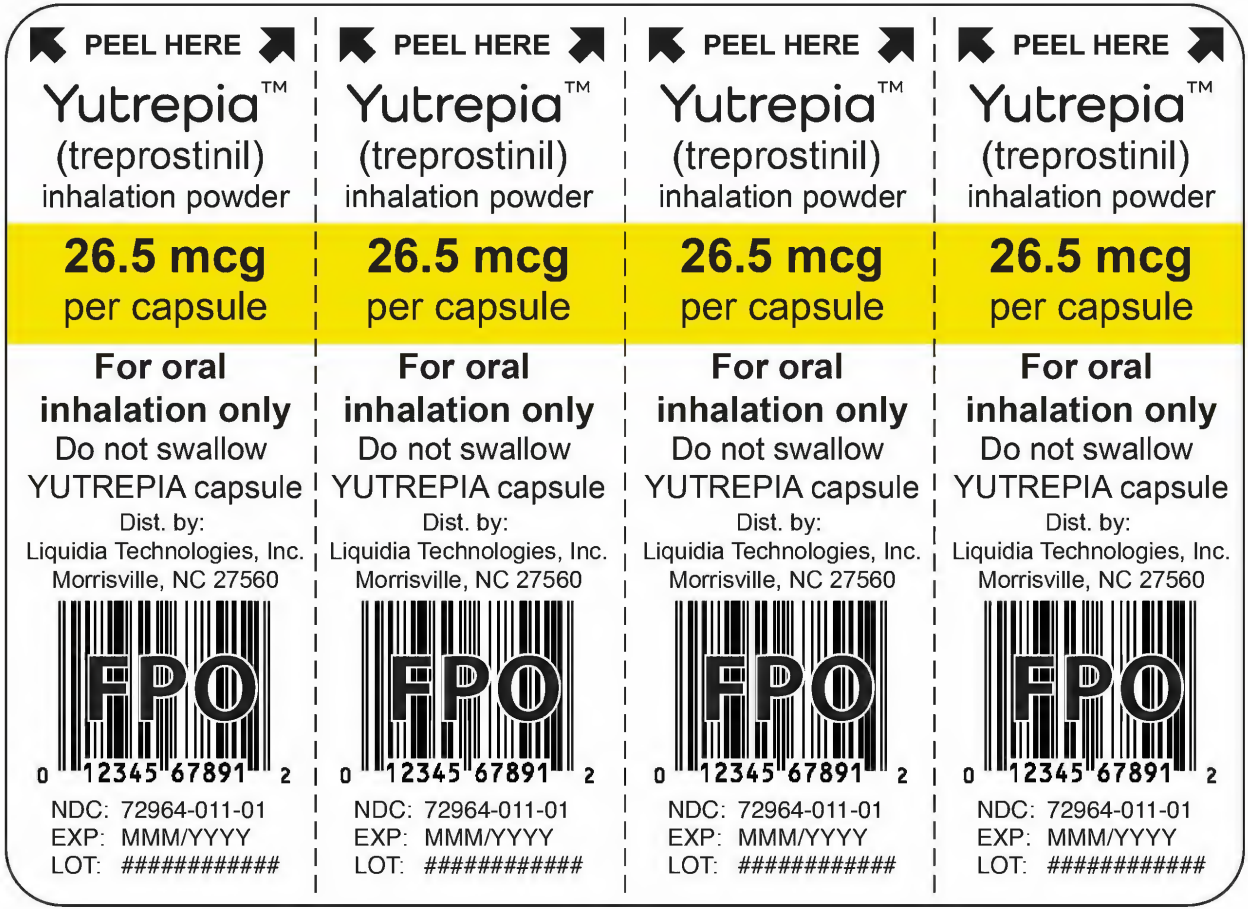
Issued: November 2021

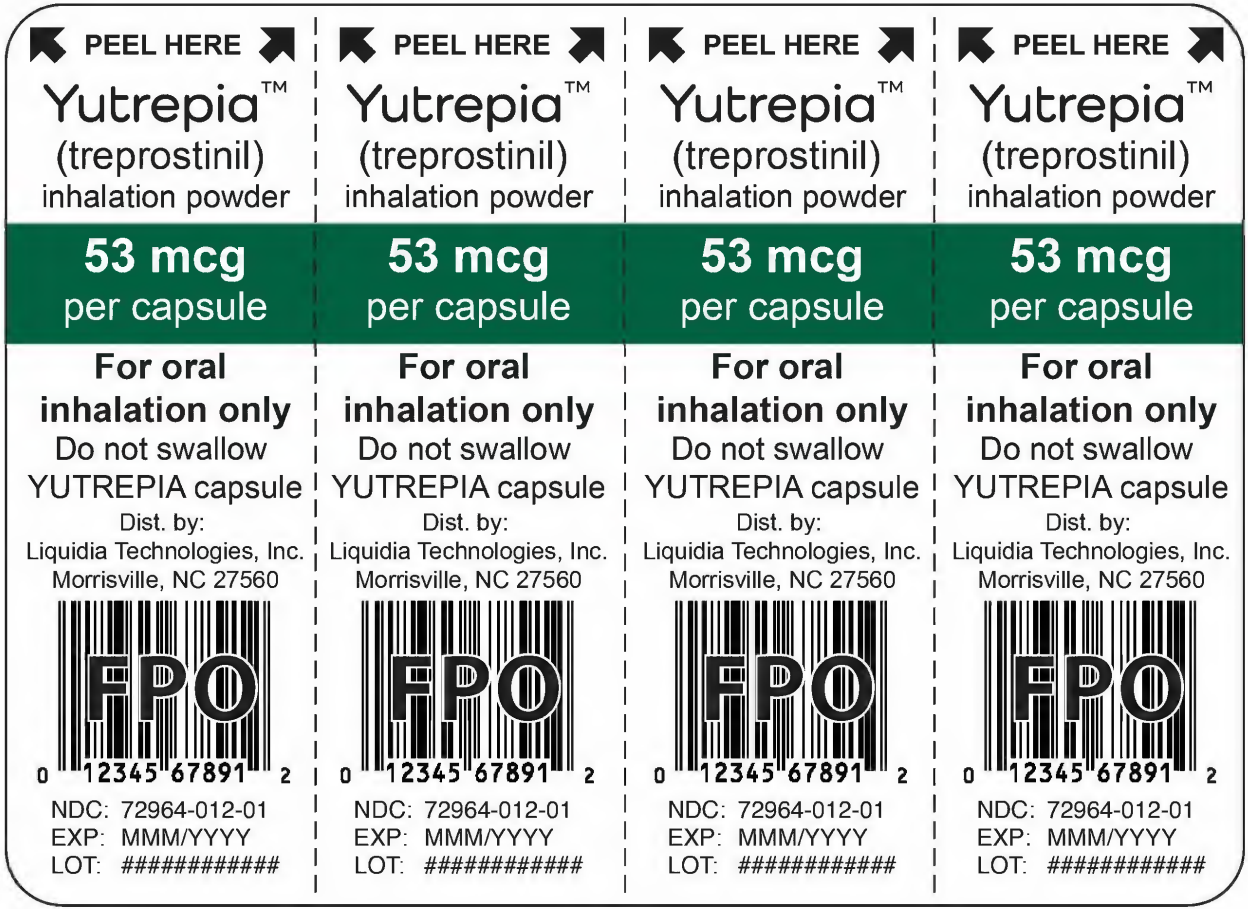
Yutrepia
(treprostinil)
inhalation powder
For oral inhalation only
DO NOT SWALLOW YUTREPIA CAPSULES
26.5 mcg
per capsule
NDC 72864-011-01
Rx Only
Read Instructions for Use before each use.
Recommended Dosage: See prescribing information.
Do not remove capsule from blister until immediately before use.
Store at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].
Keep this and all drugs out of the reach of children.
Dispensed by:
Liquidia Technologies, Inc
Morrisville, NC 27560
Liquidia
Contains:
• 28 Capsules (1 Foil Blister (each) of 4 capsules each)
• 1 Dry powder inhaler
• 7 Single-use cleaning brushes
• Instructions for Use

53 mcg per capsule
Yutrepia
(treprostinil)
inhalation powder
For oral inhalation only
DO NOT SWALLOW YUTREPIA CAPSULES
NDC 72864-012-01
Rx Only
Read Instructions for Use before each use.
Recommended Dosage: See prescribing information.
Do not remove capsule from blister until immediately before use.
Store at 68°F to 77°F (20°C to 25°C), excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].
Keep this and all drugs out of the reach of children.
Dispensed by:
Liquidia Technologies, Inc.
Morrisville, NC 27560
Liquidia
Contains:
• 28 capsules (1 Foil Mylar cards of 4 capsules each)
• 1 Dry powder inhaler
• 7 Single-use cleaning brushes
• Instructions for Use

79.5 mcg per capsule
Yutrepia
(treprostinil) inhalation powder
For oral inhalation only
DO NOT SWALLOW YUTREPIA CAPSULES
NDC 72864-013-01
Rx Only
Liquidia
Read Instructions for Use before each use.
Recommended Dosage: See prescribing information.
Do not remove capsule from blister until immediately before use.
Store at 68°F to 77°F (20°C to 25°C), excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].
Keep this and all drugs out of the reach of children.
Distributed by:
Liquidia Technologies, Inc.
Morrisville, NC 27560
Carton contains:
• 28 Capsules (1 Foil Mylar cavity of 4 capsules each)
• 1 Dry powder inhaler
• 7 Single-use cleaning brushes
• Instructions for Use

106 mcg
per capsule
Yutrepia
(treprostinil)
inhalation powder
For oral inhalation only
DO NOT SWALLOW YUTREPIA CAPSULES
NDC 72864-014-01
Rx Only
Read Instructions for Use before each use.
Recommended Dosage: See prescribing information.
Do not remove capsule from blister until immediately before use.
Store at 68°F to 77°F (20°C to 25°C); excursions permitted to 59°F to 86°F (15°C to 30°C) [see USP Controlled Room Temperature].
Keep this and all drugs out of the reach of children.
Liquidia
Distributed by:
Liquidia Technologies, Inc.
Morrisville, NC 27560
Carton:
• 28 Capsules (1 Foil Mylar cavity of 4 capsules each)
• 1 Dry powder inhaler
• 7 Single-use cleaning brushes
• Instructions for Use





PEEL HERE

Yutrepia™
(treprostinil)
inhalation powder

79.5 mcg
per capsule

For oral inhalation only
Do not swallow YUTREPIA capsule

Dist. by:
Liquidia Technologies, Inc.
Morrisville, NC 27560

0 12345 67891 2

NDC: 72964-013-01
EXP: MMM/YYYY
LOT: ###########

PEEL HERE

Yutrepia™
(treprostinil)
inhalation powder

79.5 mcg
per capsule

For oral inhalation only
Do not swallow YUTREPIA capsule

Dist. by:
Liquidia Technologies, Inc.
Morrisville, NC 27560

0 12345 67891 2

NDC: 72964-013-01
EXP: MMM/YYYY
LOT: ###########

PEEL HERE

Yutrepia™
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LOT: ###########

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Yutrepia™
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79.5 mcg
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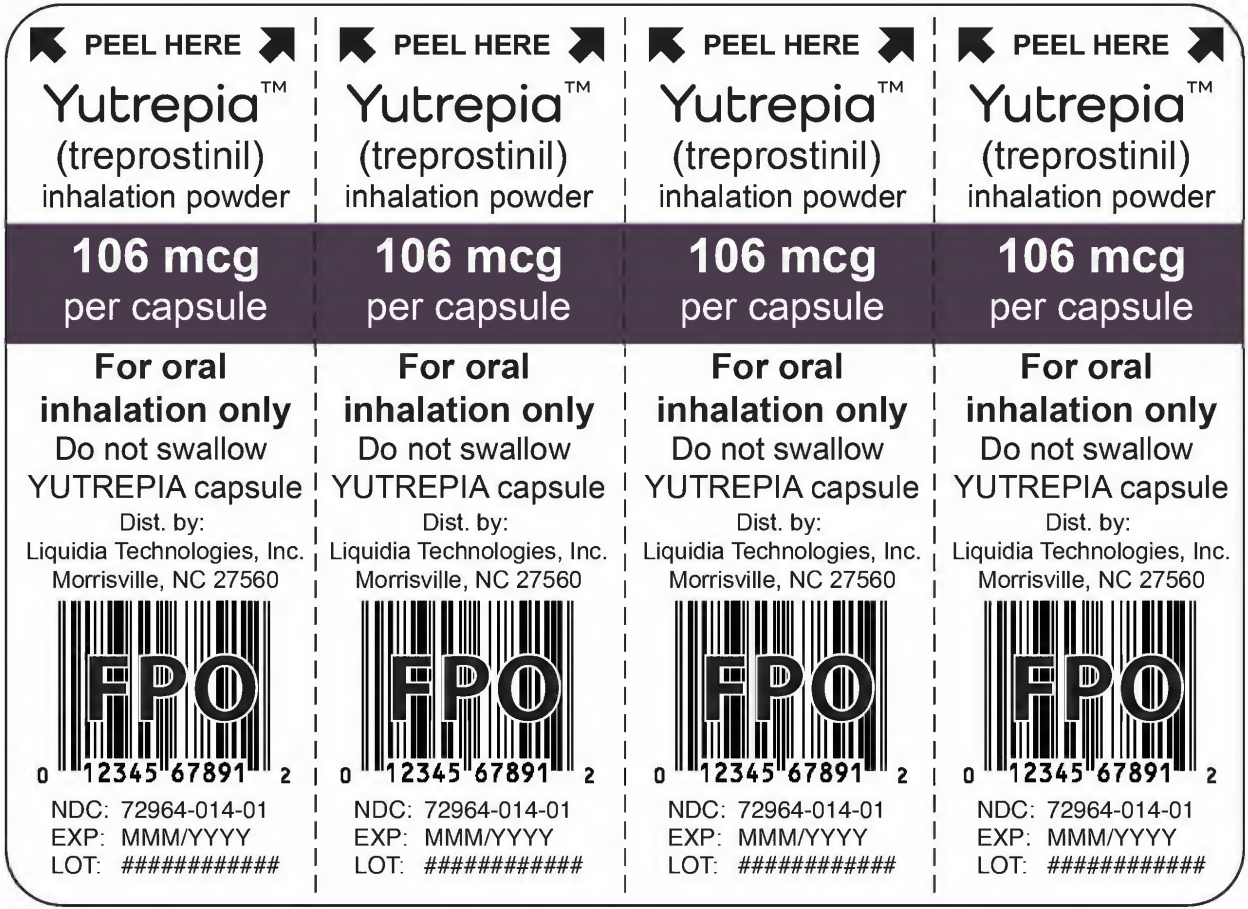
For oral inhalation only
Do not swallow YUTREPIA capsule

Dist. by:
Liquidia Technologies, Inc.
Morrisville, NC 27560

0 12345 67891 2

NDC: 72964-013-01
EXP: MMM/YYYY
LOT: ###########



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/s/

NORMAN L STOCKBRIDGE
11/04/2021 03:36:56 PM

EXHIBIT 3

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION, Plaintiff, v. LIQUIDIA TECHNOLOGIES, INC., Defendant.	Civil Action No. 20-755-RGA

TRIAL OPINION

Jack B. Blumenfeld, Michael J. Flynn, Sarah E. Simonetti, MORRIS, NICHOLS, ARSHT & TUNNELL LLP, Wilmington, DE; Huiya Wu, GOODWIN PROCTER LLP, New York, NY; William C. Jackson, Eric Levi, GOODWIN PROCTER LLP, Washington, DC; Douglas H. Carsten, Mandy H. Kim, Arthur Dykhuis, Jiaxiao Zhang, Katherine Pappas, MCDERMOTT WILL & EMERY LLP, Irvine, CA; Ian B. Brooks, Adam W. Burrowbridge, Joshua Revilla, Timothy M. Dunker, MCDERMOTT WILL & EMERY LLP, Washington, DC; Harrison Gunn, GOODWIN PROCTER LLP, Boston, MA,

Attorneys for Plaintiff.

Karen E. Keller, Nathan R. Hoeschen, SHAW KELLER LLP, Wilmington, DE; Sanya Sukduang, Jonathan Davies, Douglas W. Cheek, Adam Pivovar, Brittany Cazakoff, COOLEY LLP, Washington, DC; Erik Milch, COOLEY LLP, Reston, VA; Ivor Elrifi, COOLEY LLP, New York, NY; Deepa Kannappan, Lauren Krickl, Kyung Taeck Minn, COOLEY LLP, Palo Alto, CA,

Attorneys for Defendant.

August 31, 2022

ANDREWS, U.S. DISTRICT JUDGE:

United Therapeutics Corporation ("UTC") brought this action against Liquidia Technologies, Inc. for infringement of U.S. Patent Nos. 9,593,066 ("the '066 patent"), 9,604,901 ("the '901 patent"), and 10,716,793 ("the '793 patent") under 35 U.S.C. § 271(e)(2)(A). (D.I. 1, 16). I held a four-day bench trial. (D.I. 402–405).[1] The disputes at trial were related to the infringement and validity of claims 1, 2, 3, 6, 8, and 9 of the '066 patent and claims 1, 4, 6, 7, and 8 of the '793 patent. The '901 patent is no longer at issue.

I have considered the parties' post-trial submissions. (D.I. 406, 407, 408, 409, 411, 412, 413, 414, 415, 416, 423, 424). Having considered the documentary evidence and testimony, I make the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).

I. BACKGROUND

UTC is the holder of New Drug Application ("NDA") No. 022387 for Tyvaso®, an inhaled solution formulation of treprostinil approved for the treatment of pulmonary arterial hypertension and pulmonary hypertension associated with interstitial lung disease. (D.I. 322-1, Ex. 1, ¶¶ 5, 12). The '066 and '793 patents are listed in the FDA's Orange Book for Tyvaso®. (*Id.*, ¶ 14). The '066 patent discloses an improved process for preparing treprostinil. (*See* JTX 2). The '793 patent discloses a method of administering treprostinil by inhalation. (*See* JTX 3).

Liquidia submitted NDA No. 213005 under § 505(b)(2) of the Federal Food, Drug, and Cosmetic Act seeking FDA approval for the manufacture, use, and sale of its proposed product LIQ861 (Yutrepia™). (D.I. 322-1, Ex. 1, ¶ 2). LIQ861 is a dry powder formulation of

[1] I cite to the trial transcript as "Tr." The trial transcript is consecutively numbered.

treprostinil sodium. (*Id.*, ¶ 16). The FDA tentatively approved LIQ861 for the treatment of pulmonary arterial hypertension. (*Id.*, ¶¶ 17–18).

Liquidia's NDA contains Paragraph IV certifications alleging that both the '066 and '793 patents are invalid and/or will not be infringed by the manufacture, use, or sale of its proposed product. (*Id.*, ¶ 8). UTC received notice of Liquidia's Paragraph IV certifications and initiated the present lawsuit. (*Id.*, ¶ 9).

II. INFRINGEMENT OF THE '066 PATENT

A. Legal Standard

A patent is directly infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent." 35 U.S.C. § 271(a). Determining infringement is a two-step analysis. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). First, the court must construe the asserted claims to ascertain their meaning and scope. *Id.* The trier of fact must then compare the properly construed claims with the accused infringing product. *Id.* This second step is a question of fact. *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998). The patent owner bears the burden of proving infringement by a preponderance of the evidence. *SmithKline Diagnostics, Inc. v. Helena Lab'ys Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

In a Hatch-Waxman case, the plaintiff's infringement claim is based on the accused infringer's future conduct, rather than past acts of infringement. Under § 271(e)(2), the "infringement inquiry . . . is focused on the product that is likely to be sold following FDA approval." *Abbott Lab'ys v. TorPharm, Inc.*, 300 F.3d 1367, 1373 (Fed. Cir. 2002). "Because drug manufacturers are bound by strict statutory provisions to sell only those products that

comport with the []NDA's description of the drug, an []NDA specification defining a proposed [] drug in a manner that directly addresses the issue of infringement will control the infringement inquiry." *Id.* For product-by-process claims, the infringement inquiry is focused "on the process of making the product as much as it is on the product itself." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1370 (Fed. Cir. 2009). Thus, "a product-by-process claim is not infringed by a product made by a process other than the one recited in the claim." *Id.*

B. Asserted Claims of the '066 patent

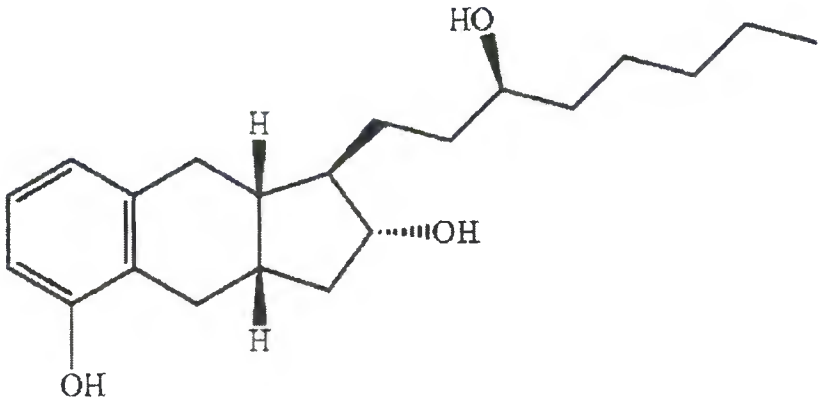
1. A pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof, said composition prepared by a process comprising providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps, forming a salt of treprostinil by combining the starting batch and a base, isolating the treprostinil salt, and preparing a pharmaceutical composition comprising treprostinil or a pharmaceutically acceptable salt thereof from the isolated treprostinil salt, whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition, and wherein said alkylation is alkylation of benzindene triol.

2. The pharmaceutical composition of claim 1, wherein the salt is isolated in crystalline form.

3. The pharmaceutical composition of claim 1, wherein the base is selected from the group consisting of sodium, ammonia, potassium, calcium, ethanolamine, diethanolamine, N-methylglucamine, and choline.

6. The pharmaceutical composition of claim 1, wherein the isolated salt is stored at ambient temperature.

8. A process of preparing a pharmaceutical product comprising treprostinil or a pharmaceutically acceptable salt thereof, comprising alkylating a triol intermediate of the formula:



hydrolyzing the resulting compound to form treprostinil, forming a salt of treprostinil stable at ambient temperature, storing the treprostinil salt at ambient temperature, and preparing a pharmaceutical product from the treprostinil salt after storage, wherein the pharmaceutical product comprises treprostinil or a pharmaceutically acceptable salt thereof.

9. A pharmaceutical product prepared by the process of claim 8.

C. Findings of Fact

1. A POSA would be either a chemical engineer or process research chemist with 3-5 years of experience in API and drug manufacturing or a master's degree in chemistry or chemical engineering who collaborated with individuals having 3-5 years of experience in API drug manufacturing.

2. Yonsung, based in South Korea, manufactures the treprostinil sodium API used to make Liquidia's LIQ861 product. (Tr. at 74:21–75:5 (Nuckolls); PTX 20 at 7). Yonsung has a Drug Master File ("DMF") for the treprostinil sodium used in LIQ861. (PTX 112 (Open DMF); PTX 201 (Restricted DMF)).

3. Yonsung synthesizes the treprostinil sodium by alkylating a batch of benzindene triol ("BTO") to provide a batch of "TN01" (PTX 201 at 7, 22, 35 (DMF Step 10)), then performing a hydrolysis step to provide a batch of treprostinil ("TN02") (*id.* at 8, 23, 36 (DMF Step 11)), and performing a salt formation step by combining the treprostinil with a base (sodium) to yield treprostinil sodium ("TN") (*id.* at 8, 24, 37 (DMF Step 12); Tr. at 75:19–76:20 (Nuckolls); Tr. at 407:2–408:21 (Winkler)).

4. LGM is a U.S. based administrative intermediary between Yonsung and Liquidia. (Tr. at 346:7–10 (Kindig); Tr. at 439:2–5 (Winkler)). Yonsung's shipments of treprostinil sodium sometimes go through LGM to Liquidia; however, LGM does not manufacture treprostinil sodium, nor is it involved in the development or administration of Liquidia's LIQ861 product. (Tr. at 331:14–21 (Kindig); Tr. at 366:5–16 (Lenox)).

5. A POSA would understand that the impurities limitations in claim 1 of the '066 patent refer to any impurities generated during the process steps of alkylating and hydrolyzing a batch of BTO (including from side reactions, impurities in reagents, solvents, or starting materials).

6. Yonsung's analytical testing of treprostinil sodium is a reliable and accurate measure of impurities in the pharmaceutical composition resulting from the alkylation and hydrolysis steps; Liquidia's processing of the TN into the pharmaceutical composition (LIQ861 bulk powder) does not affect those impurities.

7. Liquidia's proposed LIQ861 product will be prepared by a process which lowers the level of one or more impurities resulting from prior alkylation and hydrolysis steps as claimed in the '066 patent. The percentage of total "related substance" impurities and the amount of total "related substance" impurities increase during the alkylation and hydrolysis steps from BTO to the starting batch of treprostinil (TN02), and then decrease in the TN batch after the salt formation and isolation steps.

8. Liquidia's NDA and Yonsung's DMF require treprostinil sodium to be stored at 2°C to 8°C.

9. Liquidia will not use treprostinil sodium batches which have been stored at ambient temperature for GMP manufacturing.

10. Liquidia begins preparing a pharmaceutical product during Step 1 of its PRINT process.

D. Conclusions of Law

1. Claims 1, 2, and 3

Liquidia only disputes infringement of the impurities limitations in claims 1, 2, and 3. Claim 1 recites "providing a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps . . . wherein said alkylation is alkylation of benzindene triol." As a preliminary issue, the parties dispute the proper construction of "impurities resulting from prior alkylation and hydrolysis steps." Liquidia argues that the claimed impurities must result from alkylation and hydrolysis of "BTO," not the alkylation and

hydrolysis of any compound that may be present in the reaction vessel. (D.I. 411 at 3). UTC argues that the claimed impurities encompass any impurities generated during the process steps of alkylating and hydrolyzing a batch of BTO (including from side reactions, impurities in reagents, solvents, or starting materials). (D.I. 408 at 7–8).

UTC's construction is correct. The claim language requires that the impurities result from the "prior alkylation and hydrolysis *steps*." A POSA would understand that the alkylation step involves alkylating all materials in a batch of BTO, not just the single alkylation reaction of BTO. (*See* Tr. at 110:23–111:10 (Nuckolls); Tr. at 810:16–19, 818:18–22 (Scheidt); *see also* Tr. at 423:15–20 (Winkler) ("[A] real batch of – a bottle of benzindene triol could contain impurities.")). Thus, I find that a POSA would understand that any impurities generated during the alkylation and hydrolysis steps (including from side reactions) are within the scope of the claim.

Claim 1 further recites: "whereby a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition." UTC has identified the LIQ861 bulk powder as the "pharmaceutical composition" and Yonsung's TN02 as the "starting batch of treprostinil." Liquidia argues that UTC cannot prove infringement of this limitation because UTC's experts only compared the impurities between TN02 and TN, not the LIQ861 powder. (D.I. 411 at 2). UTC responds that Yonsung's impurities testing for TN is a proper measure of impurities in the pharmaceutical composition resulting from the alkylation and hydrolysis steps because Liquidia's processing of TN into LIQ861 bulk powder has no effect on the impurities from these steps. (D.I. 416 at 4). Once Liquidia receives the TN from Yonsung,

Liquidia uses its proprietary PRINT process[2] to prepare the LIQ861 bulk powder using the TN as the API. (DTX 204; PTX 20). In simple terms, Liquidia puts the TN in solution, adds excipients, and dries this formulation into the powder. (DTX 204 at 2–6; Tr. at 741:7–16 (Gonda)).

UTC's expert Dr. Nuckolls testified that he "wouldn't expect" Liquidia's processing of TN to impact the impurities from the alkylation and hydrolysis steps. (Tr. at 157:7–17 (Nuckolls); *see also* PTX 66 at 96 ("Treprostinil sodium drug substance process impurities are controlled by the manufacturer, Yonsung Fine Chemicals Co., Ltd. (Yonsung)."). Dr. Nuckolls also testified that it would be difficult for a POSA to test the impurities resulting from the alkylation and hydrolysis steps in the LIQ861 bulk powder because the composition has been mixed with other excipients. (Tr. at 133:25–134:3 (Nuckolls)). Liquidia has not provided any expert testimony to rebut these opinions; thus, I will credit Dr. Nuckolls' testimony on this point. I therefore find that the TN impurities are representative of the impurities in the "pharmaceutical composition" (LIQ861 bulk powder) resulting from the prior alkylation and hydrolysis steps. *Cf. Vectura Ltd. v. GlaxoSmithKline LLC*, 397 F. Supp. 3d 579, 587–88 (D. Del. 2019) (finding that comparison testing supported the jury's infringement verdict where there was evidence that the tested products were representative of the accused products), *aff'd*, 981 F.3d 1030 (Fed. Cir. 2020).

To prove infringement of the impurities limitations, UTC compared the (1) amount of total impurities; (2) number of total impurities; and (3) amount of *epi*-treprostinil in BTO, TN02, and TN.

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[2] PRINT stands for Particle Replication in Nonwetting Templates. (DTX 204 at 2).

First, Dr. Nuckolls analyzed the total "related substance" impurities data provided by Yonsung in its DMF. (*See* PTX 201 at 270–72).[3] For two of the three DMF validation batches (TN117I010, TN117K010), the percentage of total "related substance" impurities increased between BTO and TN02, and then decreased in TN.[4] (Tr. at 77:23–80:18 (Nuckolls); PTX 201 at 270–72; PTX 326 at 4 (identifying the corresponding BTO, TN01, and TN02 batch numbers for each TN batch number)). Dr. Nuckolls opined that these changes in the percentage of total "related substance" impurities between BTO, TN02, and TN show infringement of the impurities limitations. (Tr. at 77:23–80:18 (Nuckolls)).

Second, Dr. Nuckolls analyzed the number of total impurities detected in Yonsung's validation batches. To do so, Dr. Nuckolls looked at Yonsung's underlying high-performance liquid chromatography (HPLC) data. (Tr. at 81:8–84:19 (Nuckolls)). HPLC separates components in a mixture by running the mixture down a column. (Tr. at 81:8–23 (Nuckolls)). The mixture's components are separated based on how they interact with the column, so each component will elute at different retention times, depicted by peaks on a chromatogram. (*Id.*; Tr. at 176:3–18 (Toste)).

To determine the number of impurities, Dr. Nuckolls counted the number of HPLC peaks in the chromatograms for BTO, TN02, and TN, excluding the peaks for "the material of interest"

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[3] Because Liquidia relies on the same impurities data in its NDA, I find these data to be reliable. (*See* PTX 66 at 96; PTX 105 at 7–11).

[4] For validation batch TN117I010, the percentage of "related substance" impurities was 0.07% in BTO, 0.20% in TN02, and 0.03% in TN. (PTX 201 at 270–72). For validation batch TN117K010, the percentage of "related substance" impurities was 0.08% in BTO, 0.20% in TN02, and 0.01% in TN. (*Id.*). These results are consistent with Yonsung's acceptance criteria, which allow for a greater percentage of "related substance" impurities in TN02 than in TN. (*Id.* (2.0% for TN02; 0.5% for TN)). For validation batch TN117K020, the percentage of "related substance" impurities was 0.38% in BTO, 0.21% in TN02, and 0.01% in TN. (*Id.*).

(e.g., BTO, TN02, and TN) and for the "known impurities" that were "labeled as missing or not detected." (Tr. at 81:24–83:4 (Nuckolls)). For example, the chromatogram for TN02 for validation batch TN117I010 reported six peaks. (PTX 1540 at 79–80). One of these peaks identified TN02, which is the material of interest, not an impurity. (*Id.*). Thus, this peak was excluded from the impurities count. The chromatogram also identifies "15-epi-Treprostinil" and "Treprostinil ethyl ester" as "Peak Names," but reports these impurities as "Missing." (*Id.*). Because these known impurities were not detected in this sample, they are also excluded from the impurities count. Accordingly, Dr. Nuckolls identified three "related substance" impurities in this batch of TN02. (Tr. at 82:3–83:4 (Nuckolls)). Dr. Nuckolls testified that for two validation batches (TN117I010, TN117K010), the number of "related substance" impurities increased between BTO and TN02, and then decreased in TN.[5] (Tr. at 81:24–84:19 (Nuckolls)). Dr. Nuckolls testified that this decrease shows that one or more impurities resulting from the alkylation and hydrolysis steps are lowered from TN02 to TN. (*Id.*).

Liquidia argues that Dr. Nuckolls has failed to show a reduction in impurities "resulting from prior alkylation and hydrolysis steps . . . wherein said alkylation is alkylation of benzindene triol." (D.I. 411 at 4). Liquidia argues that the reported "total impurities" relied on by Dr. Nuckolls in his amount of total impurities analysis include "residual solvents and any impurity

[5] For validation batch TN117I010, one "related substance" impurity was identified in BTO, three "related substance" impurities were identified in TN02, and one "related substance" impurity was identified in TN. (Tr. at 82:3–83:4 (Nuckolls); PTX 1536 at 51 (BTO); PTX 1539 at 77 (TN); PTX 1540 at 79–80 (TN02)). For validation batch TN117K010, two "related substance" impurities were identified in BTO, three "related substance" impurities were identified in TN02, and one "related substance" impurity was identified in TN. (PTX 1410 at 59–62 (BTO); PTX 1157 at 33–34 (TN02); PTX 1543 at 83–84 (TN)). The underlying HPLC chromatogram for validation batch TN117K020 was not available to Dr. Nuckolls. (Tr. at 84:14–19 (Nuckolls)).

contained in the reagents or starting materials, not just impurities resulting from the claimed process steps." (*Id.*). Liquidia similarly faults Dr. Nuckolls' number of impurities analysis. Liquidia argues that since Dr. Nuckolls failed to correlate the unidentified HPLC peaks to any specific impurity, he cannot show that these impurities resulted from the alkylation and hydrolysis steps. (*Id.*).

These arguments, however, rely on Liquidia's improper interpretation of the impurities limitations. As concluded above, a POSA would understand that the claimed impurities include any impurities generated during the alkylation and hydrolysis steps, including impurities originating from starting materials or reagents. Thus, Liquidia's arguments rest on an infirm foundation.

As described in its DMF, Yonsung uses a twelve-step process to manufacture TN. (PTX 201 at 3). Step 10 of this process is the alkylation step—BTO is reacted with the alkylating agent to produce TN01. (Tr. at 75:20–76:2, 76:11–13 (Nuckolls); PTX 201 at 7). Next, in Step 11—the hydrolysis step—TN01 is hydrolyzed to produce TN02. (Tr. at 76:1–3, 13–15 (Nuckolls); PTX 201 at 8). In Step 12, TN02 is treated with a base to form TN. (Tr. at 76:3–5, 15–18 (Nuckolls); PTX 201 at 8). Thus, Dr. Nuckolls opined that any increased impurities in TN02 as compared to BTO resulted from the alkylation and hydrolysis steps, because those were the steps that were run to synthesize TN02 from BTO. (Tr. at 80:4–18, 82:3–15 (Nuckolls)). He further opined that the impurities that were generated during the alkylation and hydrolysis steps (Steps 10 and 11) were reduced during the final salt formation step (Step 12), as shown by the reduced levels of impurities in TN as compared to TN02. (*Id.*). I credit Dr. Nuckolls' testimony over Dr. Winkler's contrary testimony, which relied on Liquidia's erroneous construction. (*See* Tr. at 427:19–429:17 (Winkler)).

Based on the total impurities analyses conducted by Dr. Nuckolls, I find that UTC has proven that Liquidia will meet the impurities limitations of claim 1.[6] I therefore find that UTC has proven by a preponderance of the evidence that Liquidia's proposed LIQ861 product will infringe claims 1, 2, and 3 of the '066 patent.[7]

2. Claim 6

Claim 6, which depends from claim 1, further requires that "the isolated salt is stored at ambient temperature" before it is used to prepare a pharmaceutical composition. I construed "ambient temperature" as "room temperature (equal to or less than the range of 15°C to 30°C)." (D.I. 119). I construed "stored"/"storing"/"storage" to have its plain and ordinary meaning. (*Id.*).

Liquidia has represented to the FDA that it will store treprostinil sodium between 2°C and 8°C. Yonsung's DMF, which is incorporated in Liquidia's NDA (*see* PTX 105 at 3), specifies the following storage conditions for TN: "STORAGE: Should be kept in a tight container, protected from moisture and light and stored at 2°C to 8°C." (PTX 112 at 517). The certificates of analysis for TN and Yonsung's 2017 List of Finished and Intermediate Products also include these storage requirements. (*Id.* at 448, 450 ("Storage condition: Should be kept in a tight container, protected from moisture and light and stored at 2 °C to 8 °C (Long-term storage)."); DTX 43 at 6 (specifying TN's "Storage Conditions" as "Refrigerated")). LGM, an intermediary between Yonsung and Liquidia, stores TN in accordance with Yonsung's set

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[6] Because I find UTC's first two analyses sufficient to show infringement, I need not consider UTC's third analysis, which compares the amount of *epi*-treprostinil in TN02 and TN.

[7] "To be sure, if at the end of the day, an act that would have been an infringement . . . pertains to a patent that is shown to be invalid, there is no patent to be infringed." *Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 644 (2015). Since I ultimately conclude that claims 1, 2, and 3 of the '066 patent are invalid as anticipated, there is ultimately no infringement.

storage conditions. (Tr. at 365:23–366:4, 367:9–15, 368:2–7 (Lenox); *see also* DTX 105). Liquidia's raw material specification for treprostinil sodium states: "Storage Conditions: 2° - 8°C, protected from light and moisture." (DTX 9 at 1; *see also* Tr. at 374:12–15, 396:7–10 (Fuson) (testifying that the FDA would expect Liquidia to follow the temperature storage conditions set in its raw material specification and Yonsung's DMF); DTX 407 at 3 (FDA pre-approval inspection report wherein the FDA checked Liquidia's compliance with the 2°C to 8°C storage conditions)).

Despite these clear statements to the FDA, UTC argues that Liquidia's NDA and Yonsung's DMF permit storage of TN at ambient temperature because Yonsung's stability data show that TN is stable at ambient temperature. (*See* PTX 112 at 519–61). The parties' FDA experts Mr. Matto and Mr. Fuson both agree that if there were an out-of-specification temperature excursion (e.g., TN was exposed to ambient temperatures), Liquidia would need to conduct a full investigation before using that TN to make LIQ861. (Tr. at 272:9–274:3 (Matto); Tr. at 378:1–15 (Fuson)). But the fact that Liquidia might, in some circumstances, be permitted to use TN exposed to ambient temperatures is insufficient to show that Liquidia will do so.[8] *See Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1329 (Fed. Cir. 2010) ("[I]t is not enough to simply

[8] UTC argues that Liquidia infringes as a matter of law under *Sunovion*. (D.I. 408 at 10–11). *Sunovion* is inapposite. The patent claim at issue in that case limited the concentration of a particular isomer to "less than 0.25%," and the amended ANDA specified a product containing "[not more than] 0.6%" concentration of the same isomer. *Sunovion Pharms., Inc. v. Teva Pharms. USA, Inc.*, 731 F.3d 1271, 1274–75 (Fed. Cir. 2013). Since the ANDA specification of not more than 0.6% necessarily included products meeting the claim limitation of less than 0.25%, the Court held that Defendant had sought "FDA approval to market a generic compound within the scope of a valid patent," and thus infringed as a matter of law. *Id.* at 1280. In contrast, here, Liquidia asks the FDA to approve sales that fall outside the scope of the '066 patent. Liquidia's NDA (through incorporation of Yonsung's DMF) specifically provides that TN should be stored at 2°C to 8°C, not ambient temperature.

show that a product is capable of infringement; the patent owner must show evidence of specific instances of direct infringement.").

UTC further argues that the isolated salt (TN) used to make LIQ861 is stored at ambient temperature at three points in the process: before acceptance into Yonsung's warehouse; during shipment from Yonsung to Liquidia; and during Step 1 of Liquidia's PRINT process. (D.I. 408 at 10). I will address each argument in turn.

First, UTC asserts that TN is stored at ambient temperature in "finished product storage containers" before acceptance into Yonsung's warehouse. Relying on Yonsung's 2017 batch production record for TN117I010, Dr. Nuckolls claimed that Yonsung stored the TN at ambient temperature for 43 days between production and acceptance into the warehouse. (Tr. at 96:10–97:24 (Nuckolls); PTX 1409 at 47–50, 70). Dr. Nuckolls, however, only based his opinion on the lack of temperature notation in this batch record. The absence of temperature notation on a single batch record does not show storage at ambient temperature by a preponderance of the evidence. Rather, Yonsung's List of Finished/Intermediate Products from 2017 required TN to be stored at refrigerated temperatures. (DTX 43 at 6). Further, batch production records from 2019 indicate that TN is "refrigerated" between production and acceptance into the warehouse. (DTX 413 at 12).

Second, UTC contends that TN is stored at ambient temperature when it is shipped from Yonsung to Liquidia.[9] Three batches of TN (TN120C010, TN120G010, and TN120I010)[10]

[9] Liquidia argues that the plain and ordinary meaning of "stored" does not include shipping. (D.I. 412 at 8 n.2). I disagree. A POSA would understand that a material can be stored during shipment. (Tr. at 137:6–138:11 (Nuckolls)).

[10] These batches are not listed as "Representative Treprostinil Sodium Drug Substances Batches" in the NDA. (PTX 105 at 8).

experienced ambient temperatures for nine days during shipment from Yonsung to LGM. (PTX 19 at 17, 19–21, 26–27; Tr. at 98:1–13 (Nuckolls)). LGM notified Liquidia that these batches experienced temperature excursions, stating, "[O]ur QC released the shipment because Yonsung has long-term stability showing the Treprostinil is stable at room temperature for 6 months." (PTX 2020 at 475–78). Liquidia accepted these shipments, marking "Requirements Met" for "Transport Conditions (Temperature-if applicable)" on the receiving reports. (PTX 19 at 1; PTX 104 at 1).

UTC provides no evidence showing that Liquidia used these batches in GMP manufacturing to make a pharmaceutical composition, as is required by claim 6. Instead, the evidence shows that Liquidia only used these batches for R&D. Liquidia's Executive Director of Analytical Operation, Mr. Kindig, testified that TN120C010 was ordered specifically for use in R&D, not GMP manufacturing. (Tr. at 309:1–4, 321:1–13 (Kindig)). Mr. Kindig also testified that TN120G010 and TN120I010 were rejected by Liquidia's Quality Unit for GMP use and were relegated to R&D use only. (Tr. at 317:1–320:20 (Kindig)).[11] The fact that Liquidia accepted these out-of-specification batches instead of requesting a refund from Yonsung is not persuasive evidence of infringement, as Liquidia had another use for these batches.

UTC also asserts that three other batches of TN (TN116J010, TN117K010, and TN117I010) were stored at ambient temperature during shipment and were subsequently used for clinical trials. (*See* PTX 105 at 8 (listing these batches as "Representative Treprostinil Sodium

[11] Nevertheless, UTC again argues that the FDA will permit Liquidia to use these batches because of Yonsung's stability data. (D.I. 408 at 13–14). But, as discussed above, this does not show by a preponderance of the evidence that Liquidia will use batches exposed to ambient temperatures to prepare pharmaceutical compositions. Liquidia rejected these batches for GMP manufacturing because they were exposed to ambient temperatures, and UTC has failed to provide evidence showing that Liquidia will not continue to do so.

Drug Substances Batches")). While the temperature data loggers for these batches do show a spike to ambient temperature, this spike directly corresponds with Liquidia's receipt of the batches. (PTX 116; PTX 117; Tr. at 324:11–327:24 (Kindig); Tr. at 150:17–153:22 (Nuckolls) (confirming that receipt date and spike date were both December 11, 2017)). Once Liquidia receives the TN shipment, an employee will open the box, set aside the data logger and paperwork, and transfer the TN to the GMP refrigerator. (Tr. at 321:18–323:7 (Kindig)). Because the temperature logger does not automatically stop once the box is opened, the employee will later press the button to stop the data logging when dealing with the paperwork. (Tr. at 322:15–323:2; 327:18–328:8 (Kindig)). This explains why the data loggers immediately spiked into ambient temperature on the date Liquidia received and opened the box. Thus, the temperature data loggers for these three batches do not prove storage at ambient temperature.

The remaining shipments that UTC points to did not include temperature data loggers. (PTX 123; PTX 124; PTX 127; PTX 823; *see also* PTX 126 at 24 (temperature logger showing a maximum temperature of 6.1°C)). Contrary to UTC's assertion, the lack of temperature data is not persuasive evidence that these batches were stored at ambient temperature.

Third, UTC argues that TN is stored at ambient temperature in a drybox during Step 1 of Liquidia's PRINT process. Liquidia's PRINT process has six steps: (1) "Preparation of aqueous stock solution"; (2) "Preparation of engineered particles (particle fabrication)"; (3) "Dry collection of engineered particles as bulk LIQ861 inhalation powder"; (4) "Drying and packaging of bulk LIQ861 inhalation powder"; (5) "Drug Product Primary Packaging – encapsulation of bulk LIQ861 inhalation powder in [HPMC] capsules"; and (6) "Drug Product Secondary Packaging – blister packaging and assembly of commercial drug product kit." (DTX

204 at 2). After Step 4, the LIQ861 bulk powder is shipped to Xcelience for encapsulation and packaging (Steps 5 and 6). (*Id.* at 12).

During Step 1, a sample of TN is placed in a drybox and used to make a stock aqueous solution. (PTX 70 at 9–17). Dr. Nuckolls claims that TN is "stored" in the drybox for three hours. (Tr. at 99:24–100:7 (Nuckolls) (relying on the time stamps in Step 2-2 (8:12am) and Step 2-17 (11:46am) of the Batch Production Record (PTX 70))). A POSA, however, would understand that TN is being used, not stored, during Step 1 of the PRINT process. (*See* DTX 204 at 2 (referring to the PRINT process as "[t]he manufacturing process"). Thus, evidence that Liquidia places TN in a drybox does not prove infringement of the storage limitation.

Liquidia has represented to the FDA that it will store treprostinil sodium at 2°C to 8°C. UTC has failed to prove that Liquidia will go against these representations and store isolated treprostinil sodium at ambient temperature before it is used to prepare a pharmaceutical composition. *See In re Brimonidine Pat. Litig.*, 643 F.3d 1366, 1378 (Fed. Cir. 2011) ("We cannot assume that [the NDA filer] will not act in full compliance with its representations to the FDA."). Accordingly, I find that UTC has failed to prove by a preponderance of the evidence that Liquidia's proposed LIQ861 product will infringe claim 6.

3. Claims 8 and 9

Liquidia only disputes infringement of the temperature storage limitation in claims 8 and 9. Claims 8 and 9 require "storing the treprostinil salt at ambient temperature, and preparing a pharmaceutical product from the treprostinil salt after storage." UTC asserts that the three instances of storage discussed above with respect to claim 6 apply equally to claims 8 and 9. (D.I. 408 at 16). This evidence fails to show storage of TN at ambient temperature for the reasons discussed above.

Because claims 8 and 9 require storage of "the treprostinil salt," whether isolated or not, UTC points to three additional instances of storage at ambient temperature to show infringement. Specifically, UTC contends that the LIQ861 bulk powder, which contains the treprostinil salt after it is mixed with excipients, is stored at ambient temperature between PRINT Steps 1 and 2; between PRINT Steps 2 and 3; and between PRINT Steps 3 and 4. (*Id.*).

Claim 8 recites a method for "preparing a pharmaceutical product," while claim 6 recites a "pharmaceutical composition." UTC contends that the LIQ861 bulk powder is the "pharmaceutical composition" and LIQ861 is the "pharmaceutical product." (*Id.*). UTC asserts that Liquidia prepares the pharmaceutical composition during PRINT Steps 1–4 and begins "preparing a pharmaceutical product" at PRINT Step 5. (*Id.*). I disagree. I find that a POSA would understand that Liquidia begins preparing the LIQ861 product at PRINT Step 1, not Step 5.[12] Steps 5 and 6 simply involve encapsulating and packaging the LIQ861 inhalation powder produced in Step 4, i.e., putting it in final dosage form. (Tr. at 455:9–12 (Winkler); DTX 204 at 2). A POSA would understand that the encapsulation and packaging performed during these steps would not change the chemical properties of the bulk LIQ861 inhalation powder produced in Step 4. (Tr. at 455:5–18 (Winkler)). Accordingly, a POSA would understand that Liquidia begins preparing a pharmaceutical product before the final packaging steps.

Any "storage" between steps in the PRINT process thus cannot meet the limitations of claims 8 and 9, which require storage before preparing a pharmaceutical product. I therefore

[12] While I agree with UTC that a POSA would understand the "pharmaceutical product" of claim 8 to be distinct from the "pharmaceutical composition" of claim 6, this does not mean that the preparation of the pharmaceutical composition and pharmaceutical product cannot begin at the same point.

find that UTC has failed to prove infringement of claims 8 and 9 by a preponderance of the evidence.[13]

III. INVALIDITY OF THE '066 PATENT

A. Product-by-Process Claims (Claims 1, 2, 3, 6, and 9)

1. Legal Standard

"In determining validity of a product-by-process claim, the focus is on the product and not on the process of making it." *Amgen Inc. v. F. Hoffman-La Roche Ltd*, 580 F.3d 1340, 1369 (Fed. Cir. 2009). "That is because of the . . . long-standing rule that an old product is not patentable even if it is made by a new process." *Id.* at 1370. "If the product in a product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." *In re Thorpe*, 777 F.2d 695, 697 (Fed. Cir. 1985). However, there is an exception to this general rule when "the process by which a product is made imparts 'structural and functional differences' distinguishing the claimed product from the prior art." *Greenliant Sys., Inc. v. Xicor LLC*, 692 F.3d 1261, 1268 (Fed. Cir. 2012) (quoting *Amgen*, 580 F.3d at 1370). "The party asserting anticipation bears the burden of proving that the process limitations do not result in an invention distinguishable from the prior art." *Cubist Pharms., Inc. v. Hospira, Inc.*, 75 F. Supp. 3d 641, 668 (D. Del. 2014) (citing *Amgen*, 580 F.3d at 1370), *aff'd*, 805 F.3d 1112 (Fed. Cir. 2015).

2. Findings of Fact

1. The priority date of the '066 patent is December 17, 2007.

[13] Liquidia also argues that UTC has failed to show that Liquidia uses "a salt of treprostinil stable at ambient temperature" as required by claims 8 and 9. (D.I. 411 at 12). Because I have found that UTC has failed to prove infringement of the storage limitation, I need not address this argument.

2. Treprostinil is also known as UT-15 or treprostinil free acid. (DTX 258 at 1; DTX 674 at 4; Tr. at 408:16–17, 459:5–6, 461:5–6 (Winkler); Tr. at 742:5–9 (Gonda)).

3. A 2004 *Journal of Organic Chemistry* article by Moriarty et al., in relevant part titled "Synthesis of UT-15 (Treprostinil)" ("Moriarty"), teaches the synthesis of 99.7% pure treprostinil free acid, via alkylation and hydrolysis.

4. Moriarty is prior art.

5. The UT-15 treprostinil taught by Moriarty is the same chemical structure as the treprostinil product of claims 1–3, 6, and 9 of the '066 patent.

6. The average purity of UTC's batches of UT-15 treprostinil made by Moriarty and the '066 process are the same: 99.7%.

7. There are no structural or functional differences between the UT-15 treprostinil taught by Moriarty and the treprostinil claimed in the '066 patent.

3. Conclusions of Law

Claims 1, 2, 3, 6, and 9 are product-by-process claims, which claim a "pharmaceutical composition[/product] comprising treprostinil or a pharmaceutically acceptable salt thereof." Liquidia argues that these claims are invalid because the claimed product is the same product previously disclosed in the prior art by the 2004 Moriarty publication.[14] (D.I. 406 at 3).

[14] UTC faults Liquidia for failing to assert Moriarty as a § 102(a) anticipating reference. (D.I. 413 at 14 & n.10). This argument misunderstands Liquidia's invalidity theory. Liquidia claims that Moriarty anticipates under product-by-process law, not that Moriarty anticipates the claimed process steps. UTC did not object to the admission of evidence relating to this anticipation theory at trial. Thus, UTC cannot now argue that Moriarty is not prior art because Liquidia failed to disclose it as such. UTC also (newly) argues that Liquidia has failed to show that Moriarty was enabled. (*Id.* at 15–16). However, it is UTC's burden to prove that Moriarty is not enabled. *Apple Inc. v. Corephotonics, Ltd.*, 861 F. App'x 443, 450 (Fed. Cir. 2021) (nonprecedential) ("[R]egardless of the forum, prior art patents and publications enjoy a presumption of enablement, and the patentee/applicant has the burden to prove nonenablement for such prior art."); *In re Antor Media Corp.*, 689 F.3d 1282, 1289 (Fed. Cir. 2012) ("[D]uring patent prosecution, an examiner is entitled to reject claims as anticipated by a prior art publication or patent without conducting an inquiry into whether or not that prior art reference is enabling. As long as an examiner makes a proper prima facie case of anticipation . . . , the burden

The 2004 article published in the *Journal of Organic Chemistry* by Robert M. Moriarty et al., entitled, in relevant part, "Synthesis of UT-15 (Treprostinil)" ("Moriarty"), teaches the synthesis of treprostinil free acid by alkylation and hydrolysis of BTO. (DTX 258 at 8; Tr. at 461:17–25 (Winkler)). Liquidia argues that the treprostinil product claimed in the product-by-process claims is identical to the treprostinil free acid of Moriarty.

As a preliminary matter, UTC argues that Moriarty cannot invalidate the product-by-process claims because it only discloses treprostinil, not a "pharmaceutical composition[/product] comprising treprostinil." (D.I. 413 at 8–9). The '066 patent, however, makes no distinction between treprostinil and a pharmaceutical composition/product comprising treprostinil. The specification only describes the steps for synthesizing treprostinil or treprostinil salt. (*See* JTX 2 at 9:46–14:54 (Examples 1–5), 17:23 (Example 6, step 51, final yield is "UT-15"); *see also id.* at 5:57–59 ("The present invention provides for a process for producing treprostinil and other prostacyclin derivatives and novel intermediate compounds useful in the process.")). There is no description of combining treprostinil or treprostinil salt with excipients. Thus, a POSA reading the '066 patent specification would understand that treprostinil is a "pharmaceutical composition[/product] comprising treprostinil." This reading is confirmed by the testimony of both parties' experts. (Tr. at 104:22–105:8 (Nuckolls) (stating that the pharmaceutical composition in claim 1 "could be Treprostinil or the pharmaceutically acceptable [salt thereof]"); Tr. at 462:15–24 (Winkler) (confirming that the product claimed by the product-by-process claims "could just be Treprostinil")).

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shifts to the applicant to submit rebuttal evidence of nonenablement."). UTC has failed to submit such evidence.

Liquidia's expert Dr. Winkler testified that the UT-15 treprostinil disclosed in Moriarty and the '066 treprostinil were structurally and functionally the same. (Tr. at 457:6–480:2 (Winkler)). Specifically, the UT-15 treprostinil disclosed in Moriarty has the same chemical structure as the treprostinil product of claims 1, 2, 3, 6, and 9. (Tr. at 462:25–463:2, 467:3–5 (Winkler). *Compare* DTX 258 at 3 (depicting the chemical structure of UT-15 treprostinil as compound 7), *with* JTX 2 at 14:20–30 (depicting the chemical structure of treprostinil)). Claims 1, 2, 3, 6, and 9 do not claim any purity percentage, impurity profile, or commercial scale production.[15] (Tr. at 460:8–16 (Winkler)). The specification discloses that the treprostinil generated by the claimed process has a purity ranging from 99.7% to 99.9%. (JTX 2 at 14:55–65). The patent further advises, "In one embodiment, the purity of [treprostinil free acid] is at least 90.0%, 95.0%, 99.0%, 99.5%." (*Id.* at 9:22–23). The UT-15 treprostinil disclosed in Moriarty has a purity of 99.7%, which falls within the disclosures of the '066 patent specification. (DTX 258 at 13; Tr. at 462:9–14 (Winkler)).

Dr. Winkler also testified that UTC manufactured UT-15 treprostinil according to both processes. (Tr. at 463:20–22 (Winkler)). He testified that UTC used the Moriarty process in Chicago starting in 1997,[16] and in 2007, UTC moved the manufacturing process to Silver

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[15] UTC argues that the claim limitation requiring that the "level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition" defines the claimed product. (D.I. 413 at 7–8 (citing *In re Nordt Dev. Co.*, 881 F.3d 1371, 1376 (Fed. Cir. 2018))). I disagree. This impurities limitation is a process limitation that requires comparing the level of certain process impurities in the starting batch of treprostinil and the pharmaceutical composition, as shown in the infringement analysis above. This limitation merely describes the process and does not impart any structural or functional differences in the claimed pharmaceutical composition (as shown in Dr. Winkler's analysis discussed *infra*). *See In re Nordt*, 881 F.3d at 1375–76; *Greenliant*, 692 F.3d at 1268–69.

[16] UTC argues that Dr. Winkler failed to show that UTC's former Chicago process was the same process disclosed in Moriarty. (D.I. 413 at 17–19). In reaching this conclusion, Dr. Winkler compared the Moriarty paper and the description of the Chicago process and determined that

Spring, Maryland and changed to the '066 process. (Tr. at 464:15–465:2 (Winkler) (citing DTX 627A); Tr. at 546:1–4 (Batra); DTX 619). UTC told the FDA that the products made by both processes were the "same" and "equivalent." (DTX 70 at 3 ("[T]he lots of treprostinil API produced by the new process in Silver Spring are of the same high quality and purity as the commercial lots of API produced by the existing process at the Chicago facility."); DTX 619 at 10 ("The release data for the drug substance batch prepared by the revised route of synthesis indicate that it is of equivalent quality to the batches produced by the current synthetic route, particularly with respect to the assay and purity profile."); DTX 646 at 4–5 ("[T]he simplified chemical synthesis of treprostinil will provide API that meets the same acceptance criteria as API obtained from the 20-step chemical synthesis, with a very similar impurity profile and similar acceptance criteria.")).

UTC used both processes to make treprostinil free acid for its drug Remodulin®. (Tr. at 467:17–468:3 (Winkler); Tr. at 545:7–19 (Batra); JTX 2 (titled "Process to Prepare Treprostinil, The Active Ingredient in Remodulin®")). UTC never represented to the FDA that the UT-15 treprostinil made according to the '066 patent in Silver Spring was safer, less toxic, or purer than the UT-15 treprostinil made according to Moriarty in Chicago. (Tr. at 469:7–14, 478:23–479:21 (Winkler)). Based on this, Dr. Winkler concluded that a POSA would understand there not to

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they recited the same reactions. (Tr. at 519:18–22, 520:9–21 (Winkler)). Dr. Winkler also relied on one of the inventors, Dr. Batra, who testified that "Moriarty's process" "might be one of the terms" used to describe the Chicago process. (Tr. at 546:5–10 (Batra); *see also* JTX 2 at 1:28–31 ("Treprostinil, and other prostacyclin derivatives have been prepared as described in Moriarty . . . .")). No UTC witness disputed Dr. Winkler's statement that the Moriarty process was used in Chicago. In fact, UTC's witnesses relied on documents comparing the Chicago and Silver Spring products to demonstrate a structural difference. (*See* Tr. at 783:21–786:17 (Bunce); Tr. at 793:16–794:12, 799:4–802:19 (Walsh)). I therefore credit Dr. Winkler's testimony that the "Chicago process" and "Moriarty process" are the same.

be any "efficacy, toxicity," or "biological activity" differences between the treprostinil made according to Moriarty and the '066 treprostinil. (Tr. at 479:12–21 (Winkler)).

Dr. Winkler further testified that UTC had identical specification limits (with respect to unidentified impurities, identified impurities, and total related substances) on allowable impurities between the two processes' products. (Tr. at 469:15–471:23 (Winkler). *Compare* DTX 151 at 1 (Silver Spring Product Certificate of Analysis from 2020), *and* DTX 627A at 5–6 (Silver Spring Process Optimization Batches Release Testing Data), *with* DTX 627A at 7 (Chicago Release Testing Data)). UTC increased its purity assay range from 97–101% (Chicago) to 98–102% (Silver Spring). (Tr. at 784:23–786:9 (Bunce); DTX 70 at 3; DTX 151 at 1; DTX 627A at 7). But Dr. Winkler testified that the purity of 96 batches of treprostinil made by the Chicago process was 98.9%–100.3%, within both the 97–101% and 98–102% ranges. (Tr. at 470:21–473:5 (Winkler)). Dr. Winkler testified, and UTC did not refute, that the average purity of UTC's batches of UT-15 treprostinil made by the Chicago process and the Silver Spring process were the same: 99.7%. (Tr. at 473:16–477:18 (Winkler) (relying on the purity data submitted during the IPR for UTC's U.S. Patent No. 8,497,393 (DTX 664 at App. A ("Sample of product of Moriarty process")))).

No UTC expert or fact witness rebutted Dr. Winkler's opinions or provided testimony identifying any structural or functional difference between the Moriarty treprostinil free acid and the claimed treprostinil free acid product/composition. UTC only provided evidence relating to the functional and structural differences between the Moriarty treprostinil free acid and the claimed treprostinil salt product/composition. Dr. Walsh (inventor and former UTC employee) testified that the '066 process greatly reduced the 3AU90 impurity (an isomer of treprostinil) as compared to UTC's former Chicago process. (Tr. at 793:2–794:5, 795:12–796:12, 797:11–

802:19 (Walsh)). Dr. Walsh, however, did not compare the Moriarty treprostinil free acid prepared in Chicago and the claimed treprostinil free acid product/composition. Instead, he compared the treprostinil free acid prepared at the Chicago facility and the treprostinil diethanolamine salt prepared by the '066 process. (Tr. at 803:1–12 (Walsh)). Dr. Walsh confirmed that treprostinil diethanolamine salt is a different compound from treprostinil free acid. (Tr. at 804:17–19 (Walsh)). Thus, Dr. Walsh's testimony fails to identify any structural or functional differences between the treprostinil products.

UTC also argues that the '066 patent's "capability for making a pharmaceutical composition from treprostinil salt that had been stored at ambient temperature is novel over the prior art." (D.I. 413 at 24). UTC is improperly focusing on the process limitations of the claims. The storage and stability limitations in claims 6 and 9 relate to the intermediate salt generated during the process steps, not the final composition/product. The claims do not cover any stability or storage of the final treprostinil product. Nor is this "capability" a structural or functional difference which appears in the claimed product. Instead, UTC admitted that the claimed treprostinil free acid was not stable at room temperature, which presents no improvement over the Moriarty UT-15 treprostinil. (Tr. at 964:19–965:7 (UTC Closing)).

The product-by-process claims recite a "pharmaceutical composition[/product] comprising treprostinil *or* a pharmaceutically acceptable salt thereof." Thus, if the treprostinil product is anticipated, then the claims are invalid, regardless of whether the treprostinil salt is anticipated. *See Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001) ("When a claim covers several structures or compositions, either generically or as alternatives, the claim is deemed anticipated if any of the structures or compositions within the scope of the claim is known in the prior art."). UTC has not provided any evidence or expert testimony which compares the

claimed treprostinil free acid to the Moriarty UT-15 treprostinil, instead choosing to focus on the claimed treprostinil salt. Accordingly, there is no record evidence that contradicts Dr. Winkler's testimony that the claimed treprostinil product and Moriarty UT-15 treprostinil are the same.

Liquidia has shown by clear and convincing evidence that the claimed treprostinil product is functionally and structurally the same as the UT-15 treprostinil disclosed in Moriarty. Thus, I find that claims 1, 2, 3, 6, and 9 of the '066 patent are invalid as anticipated.

B. Written Description (Claims 1, 2, 3, and 6)

1. Legal Standard

The written description requirement contained in 35 U.S.C. § 112 requires that the specification "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc) (alteration in original). "In other words, the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.* "When determining whether a specification contains adequate written description, one must make an 'objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art.'" *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) (quoting *Ariad*, 598 F.3d at 1351).

The written description inquiry is a question of fact. *Ariad*, 598 F.3d at 1351. "A party must prove invalidity for lack of written description by clear and convincing evidence." *Vasudevan Software, Inc. v. MicroStrategy, Inc.*, 782 F.3d 671, 682 (Fed. Cir. 2015).

2. Findings of Fact

1. A POSA reading the '066 patent specification would have understood that the alkylation step results in a light brown material, the hydrolysis step

results in a pale yellow material, and the salt formation step results in an off-white material, indicating the generation and lowering of impurities from the alkylation and hydrolysis steps.

2. TLC may be used to qualitatively see the presence of impurities generated as the reaction proceeds. A POSA would have understood from the specification disclosure that monitoring the progress of a reaction by TLC would include identification of impurities generated during the reaction step.

3. Conclusions of Law

Liquidia asserts that there is no written description support for claim 1's limitation requiring that "a level of one or more impurities found in the starting batch of treprostinil is lower in the pharmaceutical composition." Claim 1 further requires "a starting batch of treprostinil having one or more impurities resulting from prior alkylation and hydrolysis steps . . . wherein said alkylation is alkylation of benzindene triol."

The specification provides adequate written description support for the impurities limitation. Specifically, the specification provides, "The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step." (JTX 2 at 17:29–32). Liquidia argues that this passage does not provide adequate written description support because it does not specify whether the impurities that are reduced are from the alkylation and hydrolysis of BTO. (D.I. 406 at 12–13). This argument, however, is based on Liquidia's narrow claim construction, which I rejected above. A POSA would understand that claim 1 encompasses any impurity generated during the alkylation and hydrolysis steps. Thus, based on this language in the specification, a POSA would understand that the inventors were in possession of the impurities limitation. (*See* Tr. at 818:1–22 (Scheidt)).

Yet, Liquidia argues that since the specification does not report the level of impurities generated during the alkylation and hydrolysis steps, the '066 patent does not provide any

written description of a "level of one or more impurities found in the starting batch of treprostinil" to compare to the pharmaceutical composition. (Tr. at 480:25–482:7 (Winkler); *see* JTX 2 at 9:49–10:37, 10:40–11:49). Liquidia argues, "[T]here is insufficient data and information in the specification of the '066 patent for a POSA to make such a comparison as claimed." (D.I. 406 at 10). This argument is not a written description argument; it might be an enablement argument. The specification need not report quantitative impurities data to provide written description support. While the '066 patent does not disclose quantitative impurities measurements, it provides qualitative measures that would alert a POSA to the generation and reduction of impurities as claimed.

As UTC's expert Dr. Scheidt testified, the '066 patent describes that the alkylation step results in a light brown material, the hydrolysis step results in a pale yellow material (i.e., the starting batch of treprostinil), and the salt formation step results in an off-white material. (Tr. at 810:13–811:1 (Scheidt); JTX 2 at 9:49–10:37 (alkylation of benzindene triol), 10:40–11:49 (hydrolysis of benzindene nitrile), 14:1–54 (conversion of treprostinil diethanolamine salt to treprostinil)). Dr. Scheidt credibly testified that a POSA would understand that these color changes indicate the generation and lowering of impurities from the alkylation and hydrolysis steps. (Tr. at 811:17–812:5, 817:5–25, 819:7–18 (Scheidt); *see also* Tr. at 484:2–8, 488:3–15, 532:16–24 (Winkler) (acknowledging that changes in color can indicate the presence of an impurity)). Liquidia faults Dr. Scheidt's analysis because the color differences do not show the specific impurity or the amount of impurity removed. (D.I. 406 at 11). This argument, however, relies on Liquidia's erroneous construction. A POSA would understand that claim 1 encompasses any impurity generated during the alkylation and hydrolysis steps. Further, the

claim simply requires the lowering of the impurities, so the specification need not disclose the specific amount of impurities removed to provide adequate written description support.

The '066 patent specification also provides that the progress of the alkylation and hydrolysis reactions were monitored by thin layer chromatography ("TLC"). (JTX 2 at 10:30–32, 11:13–16). TLC may be used to qualitatively see the presence of impurities generated as the reaction proceeds. (Tr. at 812:9–814:16 (Scheidt)). Although the patent does not disclose the use of TLC to identify or measure impurities, I credit Dr. Scheidt's testimony that a POSA would understand that the TLC would include identification of impurities generated during the reaction steps. (*Id.*).

I find that these disclosures in the '066 patent "reasonably convey[] to those skilled in the art that the inventor had possession" of the impurities limitation.[17] *Ariad*, 598 F.3d at 1351. Liquidia has not proven by clear and convincing evidence that claims 1, 2, 3, and 6 of the '066 patent are invalid for lack of written description.

[17] Liquidia relies on inventor testimony to show that the inventors did not possess the impurities limitation. (D.I. 406 at 10, 12–13). This inventor testimony does not alter my conclusion. The test for written description "requires an objective inquiry into the four corners of the specification." *Ariad*, 598 F.3d at 1351. The disclosures in the '066 patent reasonably convey possession of the claimed impurities limitation. I therefore see no reason to look beyond the four corners of the specification. *See Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 28 F.4th 1194, 1202 (Fed. Cir. 2022) (Lourie, J., dissenting from the denial of the petition for rehearing en banc) ("Where the disclosure in a patent's specification plainly corresponds to what is claimed, extrinsic evidence should not be used to cast doubt on the meaning of what is disclosed."). Even if I were to consider the inventor testimony, I would find that it does not provide clear and convincing evidence that the claims lack written description.

IV. INFRINGEMENT OF THE '793 PATENT

A. Legal Standard

"Whoever actively induces infringement of a patent shall be liable as an infringer." 35 U.S.C. § 271(b); *Warner-Lambert Co. v. Apotex Corp.*, 316 F.3d 1348, 1363 (Fed. Cir. 2003). To prevail on a claim of induced infringement, the plaintiff must show (1) "that there has been direct infringement," and (2) "that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *Enplas Display Device Corp. v. Seoul Semiconductor Co.*, 909 F.3d 398, 407 (Fed. Cir. 2018) (internal citation omitted).

In a Hatch-Waxman case, a plaintiff "can satisfy its burden to prove the predicate direct infringement by showing that if the proposed []NDA product were marketed, it would infringe the [asserted claims]." *Vanda Pharms. Inc. v. W.-Ward Pharms. Int'l Ltd.*, 887 F.3d 1117, 1130 (Fed. Cir. 2018). For method-of-treatment patents, if an NDA applicant's "proposed label instructs users to perform the patented method[,] . . . the proposed label may provide evidence of [the NDA applicant's] affirmative intent to induce infringement." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010). In that setting, the Federal Circuit has explained, "The label must encourage, recommend, or promote infringement." *Takeda Pharms. U.S.A., Inc. v. W.-Ward Pharm. Corp.*, 785 F.3d 625, 631 (Fed. Cir. 2015). Evidence that a proposed label will "inevitably lead some consumers to practice the claimed method" can suffice to support a finding of specific intent to induce infringement. *AstraZeneca*, 633 F.3d at 1060.

B. Asserted Claims of the '793 patent

> **1.** A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.

4. The method of claim 1, wherein the inhalation device is a dry powder inhaler.

6. The method of claim 4, wherein the formulation is a powder.

7. The method of claim 6, wherein the powder comprises particles less than 5 micrometers in diameter.

8. The method of claim 1, wherein the formulation contains no metacresol.

C. Findings of Fact

1. A POSA would have a medical degree with a specialty in pulmonology or cardiology, plus at least two years of experience treating patients with PH as an attending, including with inhaled therapies, or equivalent degree or experience.

2. LIQ861 is administered "3 to 5 times per day." Each administration is a single event dose.

3. LIQ861 is administered in a single event dose that is therapeutically effective.

4. Treprostinil is a vasodilator that reduces vasoconstriction in the pulmonary vasculature, causing vasodilation (widening of vasculature) and reduction of pulmonary artery pressure ("PAP") and pulmonary vascular resistance ("PVR").

5. A single administration of treprostinil will improve a patient's hemodynamics.

6. A single administration of LIQ861 will have positive hemodynamic effects, i.e., reduce PAP and PVR.

7. Liquidia has knowledge of the '793 patent.

8. Liquidia's proposed LIQ861 label teaches all elements of the asserted claims of the '793 patent.

9. Knowing that the method of administering LIQ861 is infringing, Liquidia will encourage, recommend, and promote use of LIQ861 in an infringing manner, including by providing the label, patient instructions, and additional training and other information to physicians and patients.

D. Conclusions of Law

1. Act of Direct Infringement

Liquidia argues that UTC has failed to prove that LIQ861 is administered in "a therapeutically effective single event dose," as required by claim 1 and therefore every asserted claim.[18]

Liquidia argues that claim 1 is limited to one single event dose per day rather than multiple doses per day. (D.I. 411 at 13). Liquidia reasons that claim 1 recites a "single event dose" rather than simply a "dose." (*Id.*). Liquidia's argument lacks merit. The term "single" modifies "event," not "dose." The experts agree that "single event dose" refers to a dose that is delivered in a single treatment session (i.e., a "single event"), including a session that involves multiple breaths. (Tr. at 675:4–15 (Waxman); Tr. at 704:25–705:9 (Hill)).

The claim language does not limit the number of single event doses per day. The claim recites the administration of "a" single event dose. The Federal Circuit "has repeatedly emphasized that an indefinite article 'a' or 'an' in patent parlance carries the meaning of 'one or more' in open-ended claims containing the transitional phrase 'comprising.'" *KCJ Corp. v. Kinetic Concepts, Inc.*, 223 F.3d 1351, 1356 (Fed. Cir. 2000). There is no language in the claims or specification that necessitates a departure from this general rule. *See Baldwin Graphic Sys., Inc. v. Siebert, Inc.*, 512 F.3d 1338, 1342–43 (Fed. Cir. 2008) ("An exception to the general rule that 'a' or 'an' means more than one only arises where the language of the claims themselves, the specification, or the prosecution history necessitate a departure from the rule.").

[18] Liquidia does not dispute infringement of the remaining limitations in claims 1, 4, 6, 7, and 8. (*See* D.I. 411 at 12–17).

The specification is consistent with the general meaning of "a." The specification expressly states, "Treprostinil can be administered a single time per day or several times per day." (JTX 3 at 8:1–2). Further, based on treprostinil's three- to four-hour half-life, a POSA would understand that a patient would need to receive more than one single event dose per day. (Tr. at 704:9–24 (Hill)). Accordingly, I conclude that the scope of claim 1 is not limited to one single event dose per day. I find that LIQ861 is administered in a single event dose. The proposed LIQ861 label states that LIQ861 "should be administered 3 to 5 times per day." (PTX 469 at 4). Each administration is a single event dose. (*See* Tr. at 676:15–20 (Waxman); Tr. at 705:1–9, 707:5–22 (Hill)).

The parties agree that claim 1 requires that each "single event dose" be "therapeutically effective." (Tr. at 651:5–22 (Waxman); Tr. at 683:2–9 (Hill)). The parties, however, dispute the plain and ordinary meaning of "therapeutically effective." UTC's expert Dr. Waxman testified that a therapeutically effective single event dose is one that causes a positive change in a patient's hemodynamics—i.e., "a therapeutically effective dose should cause a reduction in pulmonary artery pressure and cause a reduction in pulmonary vascular resistance." (Tr. at 651:3–22 (Waxman)). In contrast, Liquidia's expert Dr. Hill testified that a single event dose is therapeutically effective when it causes an "improvement in symptoms, in function, and/or in survival." (Tr. at 685:15–21 (Hill)). Based on the teachings of the '793 patent, I agree with Dr. Waxman that a POSA would understand the plain and ordinary meaning of "therapeutically effective single event dose" to be a dose given in a single treatment session that causes an improvement in a patient's hemodynamics (reduced PAP or PVR).

The examples in the specification studied the hemodynamic effects after a single event dose of treprostinil. (*See, e.g.*, JTX 3 at 8:57–18:11; 9:11–21 ("Pulmonary hemodynamics and

blood gases were measured at defined time points . . . . [Inhaled treprostinil sodium] doses of 30 μg, 45 μg and 60 μg reduced pulmonary vascular resistance (PVR) . . . . Reduction of PVR by a single inhalation of the two higher doses outlasted the observation period of 120 minutes."); 11:62–66 ("The application of an effective amount of treprostinil in only few or even one single breath was achieved with a highly concentrated treprostinil sodium solution.")). The examples in the patent do not report long-term measures like patient survival rate. (*See* Tr. at 702:12–20 (Hill)). A POSA reading the '793 patent would thus understand that a single event dose is therapeutically effective when it improves a patient's hemodynamics.

I find that UTC has proven by a preponderance of the evidence that LIQ861 is administered in a therapeutically effective single event dose. Treprostinil is a vasodilator that reduces vasoconstriction in the pulmonary vasculature, causing vasodilation (widening of vasculature) and reduction of PAP and PVR. (Tr. at 650:20–25 (Waxman); Tr. at 700:13–17 (Hill) (acknowledging that "the goal of using a vasodilator such as Treprostinil is to reduce the pulmonary arterial pressure and/or pulmonary vascular resistance")). Both experts agree that the '793 patent shows that the claimed single-event dosing of treprostinil improves a patient's hemodynamics. (Tr. at 637:22–25 (Waxman); Tr. at 702:1–4 (Hill) (agreeing that the '793 patent shows hemodynamic effectiveness from treprostinil); *see also* Tr. at 702:5–11 (Hill) (agreeing that on average, "a single administration of Treprostinil to someone suffering from pulmonary hypertension results in a beneficial reduction of pulmonary arterial pressure and/or vascular resistance")).

Liquidia argues that these disclosures are not evidence that a single event dose of LIQ861 will have hemodynamic effects because LIQ861 is administered in a completely different form than Tyvaso®. (D.I. 411 at 15). LIQ861 is a dry powder formulation, while Tyvaso® is a

liquid formulation delivered to the patient via a nebulizer. (Tr. at 696:6–12 (Hill)). But, as Dr. Hill acknowledged, Tyvaso® and LIQ861 involve the same molecule (treprostinil). (Tr. at 711:4–6 (Hill)). Dr. Hill testified that, because they involve the same molecule, he would expect Tyvaso® and LIQ861 to have similar effects on PAP and PVR. (Tr. at 711:4–11 (Hill); *see also* Tr. at 694:20–695:2 (Hill) (after a single event dose of LIQ861, "There might be a transient improvement in hemodynamics. There might be no effect on the hemodynamics, but in the longer term, the effect would dissipate within hours, and you would expect no therapeutic effect beyond those first few hours.")). In fact, Liquidia relied on Tyvaso®'s safety and efficacy data in its NDA. (PTX 573 at 7 ("The NDA for LIQ861 inhalational powder . . . rel[ies] on the FDA's previous finding of safety and effectiveness for Tyvaso, the selected reference listed drug (RLD) for demonstration of the effectiveness of treprostinil in the treatment of PAH."); *see also* PTX 1213 (demonstrating that LIQ861 and Tyvaso® have the same bioavailability)).

UTC's evidence shows that a single administration of treprostinil will improve a patient's hemodynamics, and thus proves by a preponderance of the evidence that a single administration of LIQ861 at the claimed doses will improve a patient's hemodynamics. I therefore find that UTC has proven by a preponderance of the evidence that the administration of LIQ861 will directly infringe claims 1, 4, 6, 7, and 8 of the '793 patent.

2. Specific Intent to Induce Infringement

Liquidia argues that it lacks specific intent to induce infringement because the proposed LIQ861 label does not encourage administration of a "therapeutically effective single event dose." (D.I. 411 at 16–17). Liquidia argues that the label does not "instruct[] that LIQ861 produces hemodynamic changes after a single event dose" because the label does not contain any

hemodynamic data or instruction to doctors to measure hemodynamic changes after a single event dose. (*Id.*). The label, however, does not need to provide hemodynamic data to induce infringement. It just needs to instruct doctors and patients to administer a single event dose that is therapeutically effective. *See AstraZeneca*, 633 F.3d at 1060 (finding that evidence that a proposed label will "inevitably lead some consumers to practice the claimed method" can suffice to support a finding of intent to induce infringement). The LIQ861 label does so by instructing doctors and patients to administer LIQ861 "3 to 5 times per day" at the claimed doses. (*See* PTX 469 at 4–6). As discussed above, UTC has proven that a single administration of LIQ861 will be therapeutically effective. Thus, the label's instructions will "inevitably lead" to the administration of a "therapeutically effective single event dose."[19] UTC has met its burden to show intent to induce infringement.

I therefore find that UTC has proven by a preponderance of the evidence that Liquidia will induce infringement of claims 1, 4, 6, 7, and 8 of the '793 patent.

On July 19, 2022, the PTAB issued a Final Written Decision in the IPR of the '793 patent, invalidating all claims of the '793 patent as obvious. *Liquidia Techs., Inc. v. United Therapeutics Corp.*, No. IPR2021-00406, 2022 WL 2820717 (P.T.A.B. July 19, 2022). Liquidia argues that it therefore cannot be liable for induced infringement under the Supreme Court's decision in *Commil*. (D.I. 427).

[19] Liquidia also argues that the label does not encourage patients to use LIQ861 as a "single event dose" because the label instructs doctors and patients to administer LIQ861 "3 to 5 times per day." (D.I. 411 at 16–17). But, as discussed above, claim 1 is not limited to one single event dose per day. The LIQ861 label instructs and encourages the administration of LIQ861 as a "single event dose."

In *Commil*, the Supreme Court held that an accused infringer's "belief regarding patent validity" is not a defense to a claim of induced infringement. *Commil USA, LLC v. Cisco Sys., Inc.*, 575 U.S. 632, 642 (2015). The Supreme Court also stated, "[I]f . . . an act that would have been an infringement or an inducement to infringe pertains to a patent that is shown to be invalid, there is no patent to be infringed." *Id.* at 644. The Supreme Court further explained, "An accused infringer can, of course, attempt to prove that the patent in suit is invalid; if the patent is indeed invalid, and shown to be so under proper procedures, there is no liability." *Id.* The Supreme Court never stated, however, that a PTAB decision invalidating patent claims in an IPR will preclude liability before it becomes final and nonappealable. *Id.* at 644–45. The Court simply stated that an IPR proceeding is one procedure through which an accused infringer can pursue an invalidity challenge. *Id.* at 645. I therefore do not think that *Commil* compels this Court to treat the '793 patent as invalid for purposes of assessing Liquidia's induced infringement. (*See* D.I. 427 at 1).

Instead, the Federal Circuit has indicated that an IPR decision does not have collateral estoppel effect until that decision is affirmed or the parties waive their appeal rights. *See XY, LLC v. Trans Ova Genetics*, 890 F.3d 1282, 1294 (Fed. Cir. 2018) ("[A]n affirmance of an invalidity finding, whether from a district court or the Board, has a collateral estoppel effect on all pending or co-pending actions."); *Papst Licensing GMBH & Co. KG v. Samsung Elecs. Am., Inc.*, 924 F.3d 1243, 1249 (Fed. Cir. 2019) (finding IPR decision became final after appeals were voluntarily dismissed). Further, the PTAB's FWD does not cancel claims. The claims are cancelled when the Director issues a certificate confirming unpatentability, which only occurs after "the time for appeal has expired or any appeal has terminated." 35 U.S.C. § 318(b); *see*

also Fresenius USA, Inc. v. Baxter Int'l, Inc., 721 F.3d 1330, 1346 (Fed. Cir. 2013) ("[I]t could hardly be clearer that Congress meant for cancellation to terminate pending suits.").

Therefore, I find that the PTAB's decision—which is not yet final—has no impact on my finding of induced infringement.

V. INVALIDITY OF THE '793 PATENT

A. Legal Standard

A patent's specification must enable the claimed invention. *In re Cortright*, 165 F.3d 1353, 1356 (Fed. Cir. 1999). For a patent claim to be enabled, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same[.]" 35 U.S.C. § 112(a). "The enablement requirement is met where one skilled in the art, having read the specification, could practice the invention without 'undue experimentation.'" *Streck, Inc. v. Rsch. & Diagnostic Sys., Inc.*, 665 F.3d 1269, 1288 (Fed. Cir. 2012) (citation omitted). Factors for assessing whether a disclosure would require undue experimentation include:

> (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988).

"Enablement is a question of law based on underlying facts." *Wyeth & Cordis Corp. v. Abbott Lab'ys*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). The party challenging validity must prove lack of enablement by clear and convincing evidence. *Cephalon, Inc. v. Watson Pharms., Inc.*, 707 F.3d 1330, 1336 (Fed. Cir. 2013).

B. Findings of Fact

1. The '793 patent has a priority date of May 15, 2006.

2. With respect to treating PH, a POSA would have a medical degree with a specialty in pulmonology or cardiology, plus at least two years of experience treating patients with PH as an attending, including with inhaled therapies, or equivalent degree or experience. With respect to inhaled formulations used in treating PH, a POSA would have a Ph.D. in pharmaceutical science or a related discipline like chemistry or medicinal chemistry, plus two years of experience in pharmaceutical formulations, including inhaled products, or equivalents (e.g., an M.S. in the same fields, plus five years of experience).

3. A POSA would understand "treating pulmonary hypertension," as claimed, to encompass treating all five WHO Groups of pulmonary hypertension ("PH"), including both isolated Group 2 (also referred to as isolated postcapillary Group 2) and pre- and postcapillary combined Group 2.

4. Treprostinil is a member of the family of compounds referred to as prostacyclins or prostacyclin analogs. (JTX 3 at 5:37–39; Tr. at 573:21–22 (Hill)). Prostacyclins dilate, or widen, the blood vessels of the lungs. (Tr. at 574:10–15 (Hill)).

5. A POSA would understand that the claimed administration of treprostinil vasodilates the pulmonary vasculature and reduces PAP and PVR, even in Group 2 PH patients.

6. The processes involved in developing dry powder formulations were well known as of 2006 and utilized routine techniques for both manufacturing and analysis.

7. Numerous dry powder inhaler ("DPI") devices were available by 2006.

8. By 2006 it was common for a POSA to develop a powder blend and then choose an available DPI for delivery of the powder formulation. Not all DPI devices need to be separately developed or specifically chosen for a given patient population.

9. Using well-known and routine techniques, Dr. Smyth prepared treprostinil free acid and treprostinil diethanolamine dry powder formulations that delivered doses within the claimed 15–90 μg range with three weeks of testing. Dr. Smyth's testing demonstrated that PH patients could effectively inhale these dry powder formulations using a DPI.

10. Selecting a suitable form of treprostinil was routine as of 2006. Methods for determining suitable forms, including salt forms, of a particular API were well known and routine for several decades prior to 2006.

11. Lactose was the only FDA-approved carrier in 2006 and was also the most common excipient for use in dry powder inhalers.

12. The Maillard reaction was well known and understood as of 2006. A POSA would have understood how to monitor any Maillard reaction between treprostinil diethanolamine and lactose.

13. Meyer (PTX 1980) was available before the priority date and discloses that PH patients were able to obtain maximum inspiratory efforts of 5.2 kPa in females and 6.8 kPa in males, which is enough to use a DPI.

C. Conclusions of Law

1. Enablement of "Treating Pulmonary Hypertension"

The asserted claims of the '793 patent recite: "A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof . . . ." Liquidia argues that the full scope of "treating pulmonary hypertension" is not enabled.

Before addressing enablement, I must first resolve the parties' claim construction dispute. Liquidia asserts that the phrase "treating pulmonary hypertension" encompasses treating all five WHO groups of pulmonary hypertension ("PH"). (D.I. 406 at 14). UTC argues that the claims are limited to treating precapillary PH. (D.I. 413 at 29–30).

PH refers to abnormally high blood pressure in the lungs. (Tr. at 562:13–14, 563:18–21 (Hill); Tr. at 629:9–630:1, 677:21–678:7 (Waxman)). PH includes a range of conditions classified in five different WHO groups: Group 1, pulmonary arterial hypertension; Group 2, pulmonary venous hypertension, i.e., PH related to left heart disease; Group 3, PH associated with disorders damaging the lungs; Group 4, PH caused by chronic thrombotic or embolic disease, including chronic blood clots in the lungs; and Group 5, a miscellaneous category for conditions that do not fit well into the other four groups. (JTX 3 at 1:41–46; Tr. at 564:19–566:7, 575:22–576:4 (Hill); Tr. at 609:18–610:11 (Rubin); DTX 385 at 2).

PH Groups 1, 3, and 4 are classified as "precapillary" PH as they are characterized by conditions affecting the pulmonary arteries or precapillary vessels. (Tr. at 564:18–566:4, 591:24–592:1 (Hill)). In contrast, the high blood pressure in the lungs of Group 2 PH patients has a different underlying cause. Defects in the left side of the heart cause elevated pressure in the postcapillary veins which reflects back as high pressure in the pulmonary arteries. (Tr. at 565:4–16, 571:17–24 (Hill)). Because the left heart is downstream (in terms of blood flow) of the pulmonary capillaries, Group 2 PH is sometimes referred to as "postcapillary" PH. (Tr. at 564:5–17, 565:4–16 (Hill); Tr. at 630:10–17 (Waxman)). Group 2 PH patients can suffer from isolated postcapillary PH or combined pre- and postcapillary PH. (Tr. at 571:10–14 (Hill); Tr. at 659:8–14 (Waxman)). In combined Group 2 PH patients, the precapillary vessels undergo changes similar to those in precapillary Group 1 PH. (Tr. at 571:10–572:8 (Hill)).

Because the cause of postcapillary PH is the left heart, not precapillary resistance, the "mainstay of treatment" by POSAs for postcapillary PH is a diuretic, not a vasodilator like treprostinil. (Tr. at 636:1–5 (Waxman); *see also* Tr. at 587:5–588:5, 600:2–9 (Hill) (stating that treating postcapillary PH patients with a vasodilator would be "stupid" because vasodilation can lead to pulmonary edema)).

Claim 1 requires "treating pulmonary hypertension comprising administering . . . treprostinil," a vasodilator. Based on this language, UTC argues that a POSA would understand claim 1 to be limited to "treating varieties of PH where using a vasodilator addresses the cause of the disease." (D.I. 413 at 30). Thus, because both experts agree that a POSA would not treat postcapillary PH with treprostinil, UTC contends that a POSA would read the claim to be limited to the treatment of precapillary PH.

This expert testimony, however, is no substitute for the clear disclosures in the '793 patent specification. The specification expressly includes all five Groups when describing "pulmonary hypertension." (JTX 3 at 1:41–45 ("Pulmonary hypertension may occur due to various reasons and the different entities of pulmonary hypertension were classified based on clinical and pathological grounds in 5 categories according to the latest WHO convention." (citing DTX 385)); *see also id.* at 1:37–38 ("Generally, pulmonary hypertension is defined through observations of pressures above the normal range . . . .")). The specification does not contain any disclosures which limit the scope of "pulmonary hypertension" to any particular subset of PH patients. Instead, the specification refers to both "precapillary pulmonary hypertension" and "pulmonary hypertension," demonstrating that the inventors viewed precapillary PH as a subset of the broadly claimed "pulmonary hypertension." (*Id.* at 9:36–37, 12:64–65, 16:64–65).

Based on these clear disclosures in the specification, I conclude that the scope of "treating pulmonary hypertension" includes treating all five Groups of PH.

Returning to enablement, Liquidia argues that it would require undue experimentation to practice the full scope of the claimed "treating pulmonary hypertension," specifically treating Group 2 PH patients. (D.I. 406 at 15–19). Dr. Hill testified that as of May 15, 2006, a POSA would have had significant safety concerns about administering inhaled treprostinil to treat Group 2 PH patients. (Tr. at 592:3–593:18 (Hill)). Several studies have indicated that Group 1 PH therapies like prostacyclins could exacerbate symptoms in Group 2 PH patients. In the FIRST trial, patients with Group 2 PH were treated intravenously with the prostacyclin epoprostenol. (Tr. at 582:12–583:23 (Hill)). Because more people died in the epoprostenol treatment group than in the control group, the study was prematurely stopped. (Tr. at 583:4–13,

585:10–14, 585:21–586:2 (Hill); DTX 358 at 1, 8–9 ("[C]hronic epoprostenol infusion in severe left ventricular failure resulted in increased mortality rates and no evidence of improved quality of life."); *see also* DTX 385 at 2 (citing the FIRST study when noting "epoprostenol therapy in patients with pulmonary venous hypertension [Group 2 PH] can be harmful")).

The label for Ventavis® (iloprost), which was the only inhaled prostacyclin approved for treatment of Group 1 PH as of May 15, 2006, similarly warned that treatment should be stopped if signs of pulmonary edema occur, as this may be a sign of pulmonary venous hypertension. (DTX 345 at 6; Tr. at 586:6–587:22 (Hill)). Dr. Hill testified that, based on this warning and the results of the FIRST trial, a POSA would have been extremely cautious about using intravenous and inhaled prostacyclins, like treprostinil, in Group 2 PH patients, as such use could create a potentially life-threatening situation in these patients. (Tr. at 587:5–588:5 (Hill)). Prostacyclins dilate the precapillary vessels, which allows more blood to flow through the capillaries and into the pulmonary veins. (*Id.*). According to Dr. Hill, this increased blood flow "could increase the pulmonary venous pressure, the pressure filling the left heart, and that increase in the capillaries can cause leakage of fluid into the gas exchanging areas of the lungs, interfering with oxygenation and creating a potentially life-threatening situation." (*Id.*).

The experts agree that the '793 patent only describes treating Groups 1, 3, and 4 PH, which are all precapillary. (*See* JTX 3 at 8:57–18:20; Tr. at 579:25–580:23, 590:25–592:2 (Hill); Tr. at 634:22–635:13 (Waxman)). Because there are no disclosures in the '793 patent or the prior art establishing the feasibility or safety of treating Group 2 PH patients with inhaled treprostinil, Dr. Hill concluded that a POSA would have had to conduct undue experimentation to treat Group 2 PH with treprostinil. (Tr. at 592:13–593:18 (Hill)). Specifically, a POSA would have had to "start at square one," conducting additional preclinical and clinical trials to

determine whether the treprostinil formulation was safe and effective in treating Group 2 PH patients. (Tr. at 593:2–18 (Hill)).

I have no doubt that a physician would have certain safety concerns about treating Group 2 PH patients—particularly isolated Group 2 PH patients—with treprostinil. (*See* Tr. at 635:16–636:10 (Waxman)). But the fact that a POSA would have safety concerns does not necessarily show a lack of enablement. The claims do not require "*safely and effectively* treating pulmonary hypertension," as Liquidia seems to be arguing. The claims instead require "treating pulmonary hypertension comprising administering . . . a therapeutically effective single event dose of a formulation comprising treprostinil."

As discussed above, a POSA would understand "a therapeutically effective single event dose" to be a dose given in a single treatment session that causes an improvement in a patient's hemodynamics (reduced PAP or PVR). Applying this construction, Liquidia has not shown by clear and convincing evidence that a POSA would have to conduct undue experimentation to practice the claimed method of treating PH.

There is no dispute that the '793 patent enables treatment of patients with Groups 1, 3, 4, and 5 PH. (*See* D.I. 406 at 16–17). The '793 patent describes the invention including the specific drug, conditions the invention is intended to treat (PH), dosages (15–90 μg), and mode and method of treatment (1–3 breaths by inhalation). (JTX 3 at 6:41–45, 7:7–12, 7:55–58, 7:64, 8:20–31, 18:1–6). The '793 patent also describes the improved hemodynamics that result from the use of the claimed invention, and the absence or reduction of side effects. (*Id.* at 8:57–18:11; Tr. at 637:22–638:3 (Waxman); Tr. at 702:1–11 (Hill)).

The record demonstrates that the claimed administration of treprostinil vasodilates the pulmonary vasculature and reduces pulmonary blood pressure, even in isolated Group 2 PH

patients. (*See* Tr. at 582:11–19, 583:14–585:23, 587:5–588:5 (Hill); Tr. at 637:18–640:5 (Waxman); DTX 358). The FIRST study, involving Flolan® (epoprostenol), showed that treating isolated Group 2 PH patients with a prostacyclin had preliminary clinical evidence of benefit and a statistically significant acute hemodynamic improvement, including a reduction of mean PAP, wedge pressure, and PVR, and improvements in exercise duration and dyspnea score. (Tr. at 582:11–19, 583:14–585:23 (Hill); DTX 358 at 1, 5–7). Thus, even with a risk of pulmonary edema, a POSA would understand that the claimed administration of treprostinil would vasodilate the pulmonary vasculature, affect hemodynamics, and treat a patient's elevated pulmonary blood pressure, i.e., treat PH. (*Id.*; JTX 3 at 1:33–40, 2:13–15, 2:30–38; Tr. at 587:5–588:5 (Hill); Tr. at 637:18–640:5 (Waxman)).

Liquidia has thus failed to show by clear and convincing evidence that it would require undue experimentation for a POSA to use treprostinil to improve a patient's hemodynamics, i.e., to treat PH as claimed. The fact that a physician might be cautious and need to monitor the patient more closely when administering treprostinil to isolated Group 2 PH patients does not change this result.

I therefore find that Liquidia has failed to show by clear and convincing evidence that claims 1, 4, 6, 7, and 8 of the '793 patent are invalid for lack of enablement.

2. Written Description of "Treating Pulmonary Hypertension"

Liquidia argues that the asserted claims of the '793 patent are invalid for lack of written description. Specifically, Liquidia contends that the '793 patent fails to convey with reasonable certainty that the inventors possessed the full scope of treating PH as claimed. Liquidia reasons that the '793 patent specification does not describe treating Group 2 PH patients with inhaled treprostinil and does not address the safety concerns that a POSA would have with respect to

treating Group 2 PH patients with treprostinil. (D.I. 406 at 19). But just like its enablement argument, Liquidia's position seems to be based on the flawed premise that the claims require "a method of safely and effectively treating pulmonary hypertension."

As the Federal Circuit has explained, to satisfy the written description requirement, "An inventor need not prove that a claimed pharmaceutical compound actually achieves a certain result. But when the inventor expressly claims that result, our case law provides that such result must be supported by adequate disclosure in the specification." *Biogen Int'l GMBH v. Mylan Pharms. Inc.*, 18 F.4th 1333, 1343 (Fed. Cir. 2021) (cleaned up). The '793 patent claims require "treating pulmonary hypertension comprising administering . . . a therapeutically effective single event dose of a formulation comprising treprostinil." The only effectiveness that is claimed is "a therapeutically effective single event dose of . . . treprostinil." The '793 patent contains adequate written description support for this claimed result.

The '793 patent describes how administering inhaled treprostinil targets the lungs, dilates the blood vessels, and reduces blood pressure. (*See* JTX 3 at 2:29–43, 3:25–5:2, 5:13–36, 8:57–18:11; Tr. at 637:22–25 (Waxman); Tr. at 702:1–11 (Hill)). Even though a POSA might have safety concerns regarding the treatment of isolated Group 2 PH patients, a POSA would understand, based on these disclosures, that treprostinil would effectively vasodilate the pulmonary vasculature, affect hemodynamics, and treat a patient's elevated pulmonary blood pressure. (*Id.*). Accordingly, these disclosures "reasonably convey[] to those skilled in the art that the inventor had possession" of the full scope of treating PH as claimed.

I therefore find that Liquidia has failed to prove by clear and convincing evidence that claims 1, 4, 6, 7, and 8 of the '793 patent are invalid for lack of written description.

3. Written Description of Dry Powder Formulations and Dry Powder Inhaler

Claim 1 of the '793 patent recites using an inhaled "formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device." The parties agree that claim 1 encompasses inhaled liquid solutions delivered via nebulizers, soft mist inhalers, and metered dose inhalers, and dry powder formulations delivered via a dry powder inhaler ("DPI"). (*See* D.I. 406 at 21; D.I. 413 at 35). Further, dependent claims 4, 6, and 7 specifically recite the use of a DPI and a powder formulation of treprostinil. Liquidia argues that the '793 patent does not provide adequate written description support for the claimed dry powder formulation of treprostinil or corresponding DPI suitable for treating PH patients. (D.I. 406 at 21).

The '793 patent specification provides, "The inhalation device can be also a dry powder inhaler. In such case, the respiratory drug is inhaled in solid formulation, usually in the form of a powder with particle size less than 10 micrometers in diameter or less than 5 micrometers in diameter." (JTX 3 at 7:22–26). Liquidia argues that this statement is nothing more than a "mere wish or plan" for a powder formulation and that the '793 patent contains no other disclosures relevant to developing a dry powder formulation of treprostinil that can be used for the claimed method of treating PH. (D.I. 406 at 22). I disagree.

The '793 patent describes the delivery of a therapeutically effective bolus dose of 15–90 μg of treprostinil by inhalation in 1–3 breaths without the expected negative side effects. (JTX 3 at Exs. 1 and 2, 17:4–24, 17:42–43, 18:4–6; Tr. at 832:19–833:6, 835:7–13, 836:17–21 (Clark)). The '793 patent demonstrates the efficacy of the claimed bolus dose by presenting data from the administration of a liquid formulation of treprostinil in 1–3 breaths using a soft mist inhaler and an ultrasonic nebulizer. (JTX 3 at Exs. 1 and 2; Tr. at 832:19–833:6 (Clark)).

Liquidia claims that this information regarding liquid formulations in the '793 patent does not inform the development of powder formulations, relying on testimony from the '793 patent inventors Drs. Rubin and Seeger. (D.I. 406 at 21). But Dr. Rubin merely stated that a solution could not be used in a DPI; he never stated that information about an inhaled solution cannot be used to develop a powder formulation. (Tr. at 612:4–5 (Rubin)). Further, Dr. Seeger merely testified, "[B]ringing something down as a powder may or may not be simply identical to bringing something down with the fluid solution." (Tr. at 297:12–23 (Seeger)). These statements are not clear and convincing evidence that information regarding liquid formulations cannot inform the development of powder formulations.

Rather, UTC's expert Dr. Clark credibly testified that the "starting point for developing a powder formulation" is determining the dose and whether it is "safe to deliver it in a single bolus." (Tr. at 833:10–20 (Clark)). Although the '793 patent does not contain any examples of dry powder formulations or DPIs, the '793 patent discloses the bolus dose and demonstrates its efficacy. The patent further states that the claimed bolus dose of treprostinil can be delivered using a DPI with a powder formulation consisting of particles less than ten microns and preferably less than five microns. (JTX 3 at 7:22–26; Tr. at 834:9–15 (Clark)). Numerous DPIs were available by 2006 and the process for developing dry powder formulations was well known and involved routine techniques. (Tr. at 758:8–10, 761:19–23 (Gonda); Tr. at 835:24–836:3, 837:19–838:1 (Clark); PTX 271 at 4; PTX 905).

Given the disclosures in the '793 patent and the state of the art, I find that a POSA would have understood that the inventors possessed a method of treating PH using a dry powder

formulation of treprostinil with a DPI.[20] (*See* Tr. at 832:19–835:16 (Clark)); *Bos. Sci. Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1366 (Fed. Cir. 2011) ("Because the specification is viewed from the perspective of one of skill, in some circumstances, a patentee may rely on information that is 'well-known in the art' for purposes of meeting the written description requirement.").

I therefore find that Liquidia has failed to prove by clear and convincing evidence that claims 1, 4, 6, 7, and 8 of the '793 patent are invalid for lack of written description.

4. Enablement of Dry Powder Formulations and Dry Powder Inhaler

Liquidia argues that the '793 patent does not enable the claimed method of treating PH patients with a dry powder treprostinil formulation and corresponding DPI. (D.I. 406 at 23–28).

The '793 patent does not provide any examples of treprostinil dry powder formulations, methods of manufacture of such powders, or DPI devices for the delivery of such formulations. (Tr. at 729:22–731:14 (Gonda); Tr. at 847:22–25 (Clark)). The processes involved in developing a dry powder formulation, however, were well known as of 2006. (Tr. at 837:19–838:1, 838:15–841:3, 842:6–844:11, 845:17–846:14 (Clark); Tr. at 864:15–865:25, 867:8–870:15 (Smyth)).

Liquidia's expert Dr. Gonda testified that to develop a treprostinil dry powder formulation, a POSA would need to (1) identify a suitable form of treprostinil; (2) identify a suitable carrier that is safe and compatible with the API; and (3) identify a suitable DPI that can

[20] Liquidia also provides inventor testimony and evidence of UTC's agreement with MannKind to show that the inventors did not possess a dry powder formulation of treprostinil as of 2006. (*See* D.I. 406 at 22 & n.4). I have found, however, that the four corners of the specification reasonably convey possession of this limitation. Thus, this extrinsic evidence is irrelevant. *See Biogen Int'l GmbH v. Mylan Pharms. Inc.*, 28 F.4th 1194, 1202 (Fed. Cir. 2022) (Lourie, J., dissenting from the denial of the petition for rehearing en banc) ("Where the disclosure in a patent's specification plainly corresponds to what is claimed, extrinsic evidence should not be used to cast doubt on the meaning of what is disclosed."); *Ariad Pharms.*, 598 F.3d at 1352 ("[T]he written description requirement does not demand . . . an actual reduction to practice[.]").

be used with the formulation to treat PH patients. (Tr. at 734:16–737:11 (Gonda)). Liquidia argues that a POSA would need to perform undue experimentation to perform these steps. (D.I. 406 at 24–25). Yet the experiments conducted by UTC's expert Dr. Smyth show otherwise.

With three weeks of testing, Dr. Smyth prepared treprostinil free acid and treprostinil diethanolamine dry powder formulations that delivered doses within the claimed 15–90 μg range. (Tr. at 863:6–864:14, 870:9–15, 876:18–879:8 (Smyth); PTX 1344; PTX 1345). Dr. Smyth used well-known and routine techniques for each step of his powder development process. (Tr. at 864:15–865:25, 867:8–876:17 (Smyth)). At a high level, Dr. Smyth's experiments involved jet milling the API several times, blending the formulations with lactose, adding the formulations to capsules, and testing the capsules using a DPI device and machine called a Next Generation Impactor, intended to mimic patient inhalation. (Tr. at 864:23–865:3 (Smyth)).

Based on this testing, I find that Liquidia has failed to prove by clear and convincing evidence that a POSA would need to perform undue experimentation to develop a treprostinil dry powder formulation. *See Bristol-Myers Squibb Co. v. Aurobindo Pharma USA Inc.*, 477 F. Supp. 3d 306, 352–53 (D. Del. 2020) (finding that defendants failed to prove lack of enablement where plaintiff's expert could successfully practice the claims), *aff'd sub nom. Bristol-Myers Squibb Co. v. Sigmapharm Lab'ys, LLC*, 858 F. App'x 359 (Fed. Cir. 2021).

First, Liquidia has failed to prove that a POSA would need to perform undue experimentation to identify a suitable form of treprostinil. The patent identifies the API to be used in the claimed invention: "treprostinil or a pharmaceutically acceptable salt thereof." (JTX 3 at claim 1; *see also id.* at 6:41–7:6 (defining what constitutes a "pharmaceutically acceptable salt" of treprostinil)). Methods for determining suitable forms, including salt forms, of a

particular API were well known and routine for several decades prior to 2006. (Tr. at 761:4–10 (Gonda); Tr. at 838:19–839:4, 841:4–21 (Clark)).

Dr. Smyth tested three forms of treprostinil: treprostinil free acid, treprostinil diethanolamine salt, and treprostinil sodium. Dr. Smyth was unable to develop a dry powder formulation of treprostinil sodium because it was too hygroscopic. (Tr. at 737:24–740:13 (Gonda); Tr. at 880:19–881:8 (Smyth)). Dr. Smyth attributed this to the lack of humidity control in his lab. (Tr. at 882:9–883:23 (Smyth)). I do not think Dr. Smyth's failure in developing a dry powder formulation of treprostinil sodium shows by clear and convincing evidence that a POSA would require undue experimentation to identify a suitable form of treprostinil. Dr. Smyth used routine techniques to determine that treprostinil sodium would not work. Further, Dr. Gonda testified that a POSA in 2006 would have a laboratory with temperature and humidity control. (Tr. at 762:4–14 (Gonda)).

Liquidia also faults Dr. Smyth's experiments with treprostinil free acid. Treprostinil free acid is not stable at room temperature and has the tendency to form dimers. (DTX 674 at 4; Tr. at 741:20–744:4 (Gonda)). Liquidia argues that despite this, Dr. Smyth did not test the stability of his treprostinil free acid powder formulation. (D.I. 406 at 27). Dr Smyth's failure to conduct additional testing is not clear and convincing evidence that undue experimentation would be required to select a suitable form of treprostinil. Dr. Gonda testified that "stability testing" was known and routine by 2006. (Tr. at 770:15–16 (Gonda)). Further, Liquidia did not perform extensive stability tests in selecting the API for LIQ861. (Tr. at 275:10–24 (Maynor)).

Second, Liquidia has failed to prove that a POSA would require undue experimentation to identify a suitable carrier. Although the '793 patent does not disclose any suitable carriers,

lactose was the only FDA-approved carrier for dry powder formulations as of 2006. (PTX 905 at 13; Tr. at 763:14–21 (Gonda); Tr. at 844:12–15 (Clark); Tr. at 866:1–4 (Smyth)). For this reason, Dr. Smyth selected lactose as the carrier for his dry powder formulations. (Tr. at 866:1–4 (Smyth)).

Dr. Gonda testified that "a POSA would have been reluctant to use lactose" as a carrier with treprostinil diethanolamine because lactose reacts with amines by the Maillard reaction. (Tr. at 754:1–11 (Gonda); *see also* DTX 481).[21] According to UTC's expert Dr. Clark, however, the Maillard reaction would not deter a POSA from attempting to formulate an amine drug with lactose unless the POSA witnessed an adverse reaction. (Tr. at 844:16–845:2 (Clark)). Dr. Clark reasoned that in 2006, the Physician's Desk Reference—which generally only describes approved drugs—described 72 examples of amine drugs formulated with lactose. (Tr. at 844:12–23 (Clark); Tr. at 866:5–867:7 (Smyth); PTX 47 at 2). Further, a POSA would have understood how to monitor any Maillard reaction between treprostinil diethanolamine and lactose. (Tr. at 844:16–845:2 (Clark); PTX 47 at 2; DTX 481 at 5). There is no evidence that Dr. Smyth noticed any Maillard reaction with treprostinil diethanolamine. (*See* Tr. at 867:22–870:15 (Smyth)). I am therefore not convinced that a POSA would require undue experimentation to select an appropriate carrier.

Third, Liquidia has not proven that identifying a suitable DPI for PH patients would require undue experimentation. A 2005 publication by Meyer et al. discloses that PH patients were able to obtain maximum inspiratory efforts of 5.2 kPa in females and 6.8 kPa in males,

[21] There is no amine in the treprostinil molecule itself, so a POSA would have no concern about the Maillard reaction with respect to combining treprostinil free acid and lactose. (Tr. at 767:23–768:8 (Gonda)).

which is enough to use a DPI. (PTX 1980 at 1; Tr. at 851:20–852:1, 852:14–854:20 (Clark)). Dr. Smyth's analytical testing involved the use of a Next Generation Impactor simulating a single breath at 4.0 kPa and 4.0L through a Plastiape RS01 low resistance inhaler (which was available as of 2006). (Tr. at 869:22–870:8 (Smyth); Tr. at 845:17–846:8 (Clark); PTX 905 at 7).[22] Dr. Smyth's testing resulted in an average emitted dose of 53.54 μg for treprostinil free acid and 52.60 μg for treprostinil diethanolamine, falling well within the claimed range of 15–90 μg. (PTX 1344 at 2; PTX 1345 at 2). Dr. Smyth's testing demonstrated that PH patients could effectively inhale his dry powder formulations using a DPI.

I find that a POSA reading the '793 patent would be able to develop a dry powder formulation of treprostinil and a corresponding DPI for treatment of PH with routine experimentation. Notably, Liquidia and its experts did not perform any experiments attempting to make dry powder formulations. Liquidia instead tries to discredit Dr. Smyth's testing. But, for the reasons discussed above, these efforts do not amount to clear and convincing evidence that a POSA would require undue experimentation. That Dr. Smyth would not administer his dry powder formulations to PH patients without conducting more studies makes no difference. (*See* D.I. 406 at 28). Of course, there is no expectation that Dr. Smyth test his formulations on actual patients for purposes of patent litigation.

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[22] Liquidia challenges Dr. Smyth's testing on the basis that he "assumed large inhaled volumes and flow rates." (D.I. 406 at 28). Dr. Smyth did not explicitly set forth his assumed inspiratory effort (4.0 kPa) and inhaled volume (4.0 L) in his testimony, but these values were set forth on a demonstrative exhibit. (DDX 5.4). Liquidia argues that these values were too high as a 2021 article by Faria-Urbina et al. reported that PAH patients have a maximum inspiratory pressure of 2.6 ± 1.2 kPa and inhale a total volume of 1.4 ± 0.03 L. (DTX 468 at 4 (Table 2); Tr. at 751:14–754:13 (Gonda); Tr. at 854:16–20 (Clark)). I nevertheless find Dr. Smyth's testing to be credible. The assumed inspiratory pressure of 4.0 kPa is consistent with the maximum inspiratory pressure reported in Meyer (5.2 kPa in females, 6.8 kPa in males). Meyer was available to a POSA as of 2006, unlike the 2021 Faria-Urbina publication.

Liquidia also argues that UTC is improperly "attempting to use a POSA's knowledge as an entire substitute for a deficient specification." (*Id.* at 26 (citing *Trs. of Bos. Univ. v. Everlight Elecs. Co.*, 896 F.3d 1357, 1364 (Fed. Cir. 2018); *Auto. Techs. Int'l, Inc. v. BMW of N. Am., Inc.*, 501 F.3d 1274, 1283 (Fed. Cir. 2007))). I do not think that is the case. The '793 patent teaches a POSA that a bolus dose of 15–90 μg of treprostinil delivered by inhalation in 1–3 breaths provides therapeutic efficacy without the expected negative side effects. (JTX 3 at Exs. 1 and 2, 17:4–24, 17:42–43, 18:4–6; Tr. at 832:19–833:6, 835:7–13, 836:17–21 (Clark); *see also* JTX 3 at 2:60–62 ("Currently, there is no treatment for pulmonary hypertension that can be administered using a compact inhalation device such as a metered dose inhaler.")). UTC's experts Dr. Smyth and Dr. Clark supplemented these disclosures by showing that a POSA at the time of the invention would have been able to use well-known and routine techniques to make the claimed dry powder formulations. *See AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) ("[T]he artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art.").

I therefore find that Liquidia has failed to prove by clear and convincing evidence that claims 1, 4, 6, 7, and 8 of the '793 patent are invalid for lack of enablement.

VI. CONCLUSION

UTC failed to prove by a preponderance of the evidence that Liquidia will infringe claim 8 of the '066 patent. Liquidia proved by clear and convincing evidence that claims 1, 2, 3, 6, and 9 of the '066 patent are invalid. UTC proved by a preponderance of the evidence that Liquidia will induce infringement of claims 1, 4, 6, 7, and 8 of the '793 patent.

The parties shall submit a final judgment consistent with this memorandum opinion within one week.

EXHIBIT 4

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)	
Plaintiff,	)	
v.	)	C.A. No. 20-755 (RGA) (JLH)
LIQUIDIA TECHNOLOGIES, INC.,	)	
Defendant.	)	

FINAL JUDGMENT

At Wilmington, Delaware, this 9th day of September, 2022:

WHEREAS, Plaintiff United Therapeutics Corporation ("UTC") commenced this action against Defendant Liquidia Technologies, Inc. ("Liquidia") asserting infringement of U.S. Patent Nos. 9,593,066 (the "'066 patent"), 9,604,901 (the "'901 patent"), and 10,716,793 (the "'793 patent") by the products that are the subject of Liquidia's New Drug Application No. 213005 seeking approval by the U.S. Food and Drug Administration ("FDA") for the manufacture, use, and sale of its proposed product LIQ861 (Yutrepia™);

WHEREAS, on January 3, 2022, the Court granted UTC's stipulation of non-infringement of the '901 patent based on the Court's construction of the claim term "contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil," with UTC preserving all rights to appeal the Court's construction of that term (D.I. 278);

WHEREAS, at trial, UTC asserted infringement of claims 1, 2, 3, 6, 8, and 9 of the '066 patent and claims 1, 4, 6, 7, and 8 of the '793 patent against Liquidia, and Liquidia asserted counterclaims of non-infringement and invalidity of those claims;

WHEREAS, the Court held a bench trial in the above-captioned action on March 28 to March 31, 2022; and

WHEREAS, the Court issued a Trial Opinion setting forth its Findings of Facts and Conclusions of Law on August 31, 2022 (D.I. 433);

IT IS HEREBY ORDERED AND ADJUDGED:

1. Judgment is hereby entered in favor of Liquidia and against UTC that claims 1, 2, 3, 6, and 9 of the '066 patent are invalid for the reasons set forth in the Court's Trial Opinion of August 31, 2022 (D.I. 433);

2. Judgment is hereby entered in favor of Liquidia and against UTC that Liquidia's proposed LIQ861 product will not infringe claim 6, 8, and 9 of the '066 patent for the reasons set forth in the Court's Trial Opinion of August 31, 2022 (D.I. 433);

3. Judgment is hereby entered in favor of UTC and against Liquidia that Liquidia's proposed LIQ861 product will induce infringement of claims 1, 4, 6, 7, and 8 of the '793 patent, and that those claims are not invalid, for the reasons set forth in the Court's Trial Opinion of August 31, 2022 (D.I. 433); and

4. Pursuant to 35 U.S.C. § 271(e)(4)(A), it is hereby ordered that the effective date of any final approval by the FDA of Liquidia's New Drug Application No. 213005 shall be a date which is not earlier than the expiration date of the '793 patent.

IT IS FURTHER ORDERED:

5. In the event that any party appeals this Final Judgment, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54(d) and/or Local Rules 54.1 and/or 54.3, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and served within thirty days after final disposition of any such appeal; and

6. In the event that no party appeals this Final Judgment, any motion for attorneys' fees and/or costs under Fed. R. Civ. P. 54(d) and/or Local Rules 54.1 and/or 54.3, including any motion that this case is exceptional under 35 U.S.C. § 285, shall be considered timely if filed and

served within thirty days after the expiration of the time for filing a notice of appeal under Federal Rules of Appellate Procedure 3 and 4; and

7. Except as provided herein, all other claims and counterclaims in this action are withdrawn and dismissed with prejudice.

/s/ Richard G. Andrews
The Honorable Richard G. Andrews
United States District Judge

EXHIBIT 5

Trials@uspto.gov
571-272-7822

Paper 45
Entered: October 8, 2021

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, INC.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

IPR2020-00770
Patent 9,604,901 B2

Before ERICA A. FRANKLIN, ZHENYU YANG, and JOHN E. SCHNEIDER, *Administrative Patent Judges.*

PER CURIAM

JUDGMENT

Final Written Decision
Determining Some Challenged Claims Unpatentable
35 U.S.C. § 318(a)

Denying Petitioner's Request to Strike
37 C.F.R. § 42.5

Denying Patent Owner's Motion to Exclude
37 C.F.R. § 42.64(c)

Granting Petitioner's Motion to Submit Supplemental Information
37 C.F.R. § 42.123(b)

I. INTRODUCTION

Liquidia Technologies, Inc. ("Petitioner") filed a Petition (Paper 1 ("Pet.")), seeking an *inter partes* review of claims 1–9 of U.S. Patent No. 9,604,901 B2 (Ex. 1001, "the '901 patent"). We instituted trial to review the challenged claims. Paper 7 ("Dec." or "Decision to Institute"). Thereafter, United Therapeutics Corporation ("Patent Owner") filed a Response to the Petition (Paper 12, "PO Resp."), Petitioner filed a Reply (Paper 15), and Patent Owner filed a Sur-reply (Paper 25).

The parties filed a Joint Paper Concerning Petitioner's Request to Strike Portions of Patent Owner's Paper Nos. 12 and 25 and Exhibits 2002 and 2025. Paper 29. The parties also briefed the issues of (1) whether we should exclude Exhibits 1002 and 1012 (Papers 31, 32, 37), and (2) whether Petitioner may submit, as supplemental information, the transcript and order from the *Markman* hearing in a parallel district court case (Papers 38, 40). An oral hearing for this proceeding was held on June 23, 2021, and the transcript of that hearing is of record. *See* Paper 44 ("Tr.").

The Board has jurisdiction under 35 U.S.C. § 6 and issues this final written decision pursuant to 35 U.S.C. § 318(a) and 37 C.F.R. § 42.73. For the reasons provided below, we conclude Petitioner has established by a preponderance of the evidence that claims 1–5, 8, and 9 are unpatentable. Petitioner, however, has not established by a preponderance of the evidence that claims 6 and 7 are unpatentable.

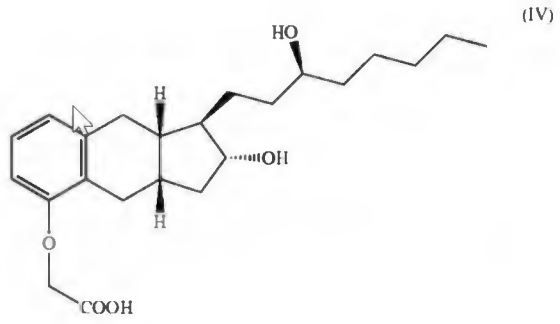
A. The '901 Patent

The '901 patent relates to "an improved process to convert benzindene triol to treprostinil via salts of treprostinil and to purify treprostinil." Ex. 1001, Abstract.

Prostacyclin derivatives are useful pharmaceutical compounds. *Id.* at 1:23–26. Treprostinil, a known prostacyclin derivative, is the active ingredient in Remodulin. *Id.* at 1:27–32. Before the '901 patent, treprostinil had been prepared as described in Moriarty[1] and other prior-art references. *Id.* According to the '901 patent, because treprostinil is "of great importance from a medicinal point of view, a need exists for an efficient process to synthesize th[is] compound[] on a large scale suitable for commercial production." *Id.* at 1:66–2:3.

The '901 patent discloses "a process for the preparation of a compound having formula IV, or a hydrate, solvate, or pharmaceutically acceptable salt thereof." *Id.* at 8:44–46. Petitioner represents that Formula IV is treprostinil. Pet. 11; Ex. 1002 ¶ 30. Formula IV has the following structure:

[1] Moriarty et al., The Intramolecular Asymmetric Pauson-Khand Cyclization as a Novel and General Stereoselective Route to Benzindene Prostacyclins: Synthesis of UT-15 (Treprostinil), 69 J. ORG. CHEM. 1890–1902 (2004) (Ex. 1009). Moriarty is one of the prior-art references asserted in this proceeding.

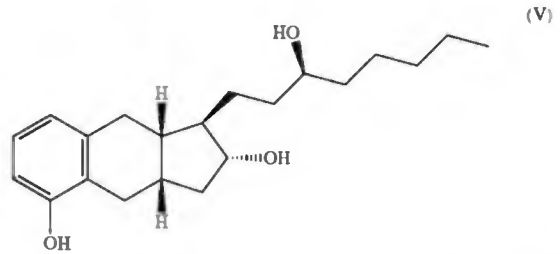


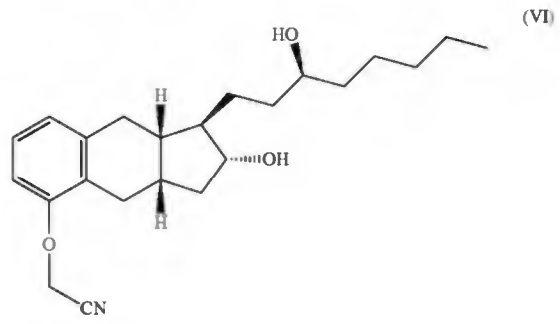
The figure above shows the structure of Formula IV. Ex. 1001, 8:48–63.

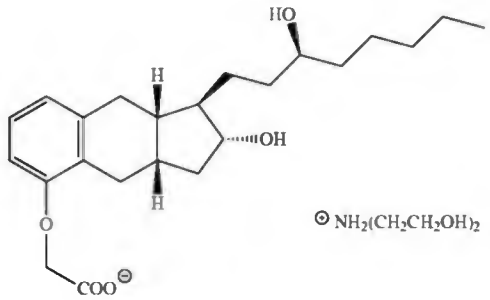
The process of the '901 patent comprises

> (a) alkylating a compound of structure V with an alkylating agent such as $ClCH_2CN$ to produce a compound of formula VI,
> (b) hydrolyzing the product of step (a) with a base such as KOH,
> (c) contacting the product of step (b) with a base B such as diethanolamine to for [sic] a salt of the following structure, and
> (d) reacting the salt from step (b) with an acid such as HCl to form the compound of formula IV.

Id. at 8:65–9:48. Structure V, formula VI, and the salt formed in step (c) have the following structures:







The figures above show the structures of structure V, formula VI, and the salt formed in step (c). *Id.* at 9:1–28, 9:33–45. The '901 patent states that "[i]n one embodiment, the purity of compound of formula IV is at least 90.0%, 95.0%, 99.0%, 99.5%." *Id.* at 9:49–50.

According to the '901 patent:

> The quality of treprostinil produced according to this invention is excellent. The purification of benzindene nitrile by column chromatography is eliminated. The impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step. Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature and can be converted to treprostinil by simple acidification with diluted hydrochloric acid, and (b) the treprostinil salts can be synthesized from the solution of treprostinil without isolation. This process provides better quality of final product as well as saves significant amount of solvents and manpower in purification of intermediates.

Id. at 16:66–17:12, *see also id.* at 6:4–18 (the same).

B. Illustrative Claim

Claim 1 is the only independent claim. With the Certificate of Correction (Ex. 1006, 2) incorporated, it is reproduced below:

> 1. A pharmaceutical batch consisting of treprostinil or a salt thereof and impurities resulting from (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution

comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the salt of treprostinil with an acid to form treprostinil, and wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.

C. Instituted Grounds of Unpatentability

We instituted trial to determine whether the challenged claims are unpatentable based on the following grounds:

Claims Challenged	35 U.S.C. §[2]	References
1–9	103(a)	Phares[3]
1–9	103(a)	Moriarty, Phares

To support their respective arguments, Petitioner relies on the Declaration of Jeffrey D. Winkler, Ph.D. (Exs. 1002, 1017) and Sylvia Hall-Ellis, Ph.D. (Exs. 1015, 1052); and Patent Owner relies on the Declarations of Rodolfo Pinal, Ph.D. (Exs. 2002, 2025).

D. Related Matters

Patent Owner asserted the '901 patent against Petitioner in *United Therapeutics Corporation v. Liquidia Technologies, Inc.*, No. 1:20-cv-00755 (D. Del.) ("the district court case"). Paper 5, 1.

Petitioner filed IPR2020-00769, challenging the claims of U.S. Patent No. 9,593,066 ("the '066 patent"), a patent in the same family as

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[2] The Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. §§ 102 and 103, effective March 16, 2013. Because the '901 patent has an effective filing date prior to March 16, 2013, we apply the pre-AIA version of § 103.

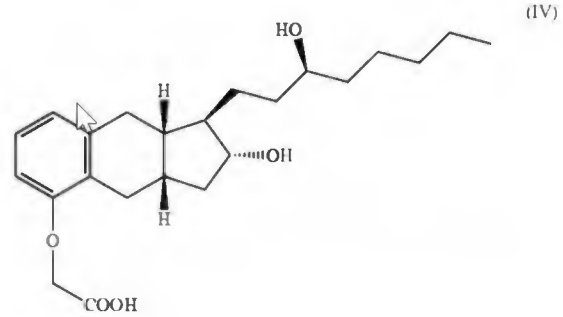
[3] PCT Application No. WO 2005/007081 A9, published Jan. 27, 2005 (Ex. 1008).

the '901 patent. *Id.* We declined to institute trial in that case. IPR2020-00769, Paper 7.

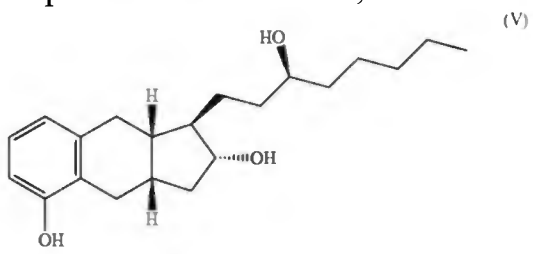
U.S. Patent No. 8,497,393 (Ex. 1004, "the '393 patent") is a parent of the '901 patent. Ex. 1001, code (63). The '393 patent is the subject of *SteadyMed Ltd. v. United Therapeutics Corp.*, IPR2016-00006 ("the '393 IPR"). The petition for the '393 IPR challenged claims 1–5, 7–9, 11–14, and 16–20 of the '393 patent as anticipated by Phares, and as obvious over Moriarty and Phares. IPR2016-00006, Paper 82 (PTAB March 31, 2017) ("the '393 Decision" or "the '393 Dec."), 7. It also challenged claims 6, 10, 15, 21, and 22 as obvious over Moriarty, Phares, and additional prior art. *Id.*

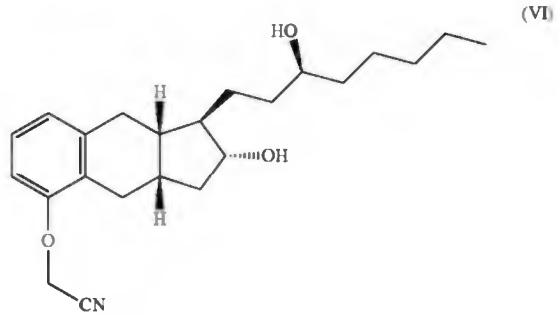
Claim 9 of the '393 patent recites:

9. A product comprising a compound of formula IV

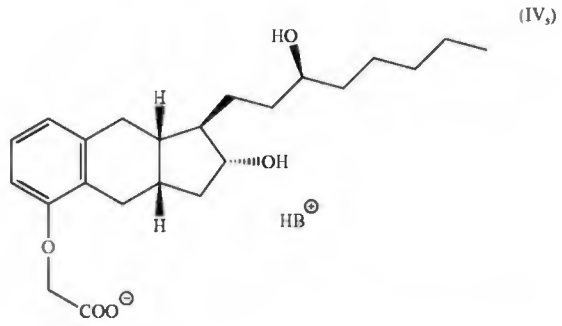


or a pharmaceutically acceptable salt thereof, wherein said product is prepared by a process comprising
(a) alkylating a compound of structure V with an alkylating agent to produce a compound of formula VI,





(b) hydrolyzing the product of formula VI of step (a) with a base,
(c) contacting the product of step [(b)] with a base B to form a salt of formula IV_s, and



(d) optionally reacting the salt formed in step (c) with an acid to form the compound of formula IV.

Formula IV of the '393 patent is the same as that of the '901 patent, and shows the structure of treprostinil. *See* the '393 Dec. 24 ("Claim 9 . . . is drawn to a product comprising the specific treprostinil compound.").

On March 31, 2017, the '393 IPR panel held that the petitioner in the '393 IPR prevailed in all asserted grounds, and that claims 1–22 of the '393 patent are unpatentable. *Id.* at 44, 67, 84, 90. Specifically, it determined that the petitioner there demonstrated the obviousness of claim 9 over the combination of Moriarty and Phares. *Id.* at 44, 68.

In reaching that conclusion, the '393 IPR panel found that "an ordinarily skilled artisan at the time of invention of the '393 patent would have had a doctorate in chemistry, pharmaceutics, pharmaceutical sciences,

medicine, or a related discipline, or a lesser degree in one of those fields, with correspondingly more experience." *Id.* at 49. It also found that the relevant skilled artisan "would have had experience in synthesizing and analyzing complex organic compounds." *Id.*

Dr. Winkler, Petitioner's expert in this proceeding, also provided testimony in the '393 IPR. He testified that "an ordinarily skilled artisan would have sought to combine Moriarty and Phares in order to eliminate the intermediate purification step taught by Moriarty, thereby increasing synthetic efficiency and lowering production costs for treprostinil diethanolamine salt." *Id.* at 46. The '393 IPR panel credited this testimony, finding that Phares teaches "intermediate purification is unnecessary to the production of treprostinil diethanolamine salt by the disclosed process." *Id.* at 47; *see also id.* at 50 ("[T]he proposed combination of Moriarty and Phares would eliminate the need for intermediate purification as required by Moriarty alone, and thereby confer efficiency and cost benefits."). Thus, it determined that "an ordinarily skilled artisan would have sought to combine Moriarty and Phares in order to reap these efficiency and cost benefits." *Id.* at 50.

The '393 IPR panel also found "an ordinarily skilled artisan would have sought to make the proposed combination for the independent reason that Phares is directed to improving treprostinil, and the Moriarty process . . . was a well-known way to make treprostinil." *Id.* It further found "an ordinarily skilled artisan would have a reasonable expectation of success in combining Moriarty and Phares." *Id.* at 52. The '393 IPR panel analyzed the evidence of objective indicia, including long-felt but unmet need and

unexpected results, but found that the evidence did not show nonobvious. *Id.* at 57–67. Thus, it concluded that the combination of Moriarty and Phares renders claim 9 of the '393 patent obvious. *Id.* at 68.

The Federal Circuit affirmed that decision. *United Therapeutics Corp. v. SteadyMed Ltd.*, 702 F. App'x. 990 (Fed. Cir. 2017).

E. The Prosecution of the '901 Patent

During the prosecution of the '901 patent, the applicant submitted the petition for the '393 IPR in an IDS. Ex. 1006, 127. Thereafter, the examiner issued an office action, rejecting then pending claims 1–3, 6, 8, and 9 as anticipated by Moriarty. *Id.* at 118. The examiner found that those claims are product-by-process claims and stated

> [E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same or obvious from the product of the prior art, the claim is unpatentable even though the prior art product was made by a different process.

Id. at 119 (quoting *In re Thorpe*, 777 F.2d 695, 698 (Fed. Cir. 1985)).

The examiner found that

> Moriarty et al disclose[s] a method for preparing treprostinil. Said method comprises the steps of: (a) alkylation of benzindene triol and (b) hydrolysis of the product of step (a) . . . . 441 g of treprostinil (a therapeutically effective amount) was prepared at 99.7% purity. Moriarty also discloses removing impurities via extraction and further purification via crystallization. Although the method of Moriarty and the steps recited in the instant claims are not identical, the product obtained is the same.

Id. at 118–19.

The examiner also rejected then pending claims 10–12 as obvious over Moriarty and Phares. *Id.* at 120. The examiner acknowledged that Moriarty fails to teach the "preparation of a diethanolamine salt of treprostinil" and the "preparation of a pharmaceutical product comprising diethanolamine salt." *Id.* The examiner, however, found "Phares et al teach[es] preparation of treprostinil diethanolamine by dissolving treprostinil acid and treating it with diethanolamine." *Id.* at 121.

According to the examiner,

> One skilled in the art practicing the invention of Phares would have found it obvious to prepare a diethanolamine salt of treprostinil prepared by the method of Moriarty. Moriarty discloses a method for preparing a treprostinil acid which is a needed starting material for the process of Phares. The resulting salt would meet the limitations directed to pharmaceutical product because treprostinil diethanolamine is the sole claimed component of the claimed pharmaceutical product.
>
> One skilled in the art would have found it obvious to prepare a pharmaceutical product from the treprostinil diethanolamine salt of Phares prepared from the treprostinil free acid that has been obtained by the process of Moriarty.

Id.

In response to the rejections, the applicant cancelled then pending claims 2 and 3, and amended other claims. *Id.* at 96–97. Most significantly, the applicant amended claim 1 as follows:

> 1. (Currently Amended) A pharmaceutical batch ~~comprising~~ consisting of treprostinil or a salt thereof and impurities resulting from ~~prepared by~~ (a) alkylating a benzindene triol, (b) hydrolyzing the product of step (a) to form a solution comprising treprostinil, (c) contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, (d) isolating the salt of treprostinil, and (e) optionally reacting the

> salt of treprostinil with an acid to form treprostinil, and~~,~~ wherein the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt.

Id. at 96.

The applicant also submitted "Patent Owner's Response and expert declarations from Dr. Williams and [Dr.] Ruffolo" from the '393 IPR. *Id.* at 98. Relying on the expert declarations, the applicant argued that "a pharmaceutical batch produced according to steps (a)-(e) of claim l is different from the product produced by the process described in Moriarty 2004" because "the processes result in products having different impurity profiles, and in fact, the pharmaceutical batch of claim 1 has higher average purity." *Id.* at 99. The applicant highlighted that

> As noted in the Patent Owner's ['393] IPR Response, the differences between claim 1's pharmaceutical batch and a product produced according to the process of Moriarty were significant enough to result in FDA's acceptance of a new purity specification for the commercial product, thus proving that the products are not the same in the eyes of the FDA.

Id. As a result, the applicant requested that the examiner withdraw the anticipation rejection. *Id.*

Regarding the obviousness rejection, the applicant contended that "the differences in the resulting products, as explained above, would not have been expected based on the prior art." *Id.* According to the applicant, "it would not have been obvious to use the salt formation step of Phares to decrease amounts of stereoisomer impurities of treprostinil" and an ordinarily skilled artisan "would have had no reasonable expectation of success in removing any undesired treprostinil stereoisomer impurities by salt formation and subsequent regeneration of the free acid." *Id.* at 99–100.

The applicant again emphasized that "even small changes in impurity are important to FDA." *Id.* at 100. Thus, according to the applicant, "FDA's decision to adopt a new purity specification for the resulting product further establishes unobviousness of the presently claimed invention." *Id.*

Thereafter, the examiner withdrew the anticipation and obviousness rejections "in view of applicants' arguments, amendments and the accompanying declarations." *Id.* at 87. And, after the applicant filed a terminal disclaimer to overcome a double-patenting rejection (*id.* at 73–75), the examiner allowed claims 1, 6, and 8–14 (*id.* at 62), and they issued as the challenged claims 1–9. The '901 patent issued on March 28, 2017, three days before the Board issued the '393 Decision.

II. ANALYSIS

A. Principles of Law

To prevail in this *inter partes* review, Petitioner "shall have the burden of proving a proposition of unpatentability by a preponderance of the evidence." 35 U.S.C. § 316(e); 37 C.F.R. § 42.1(d) (2019).

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations, including (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art;

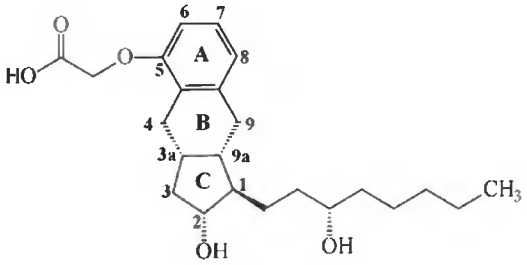
(3) the level of skill in the art; and (4) objective evidence of nonobviousness. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966); *KSR*, 550 U.S. at 406.

We analyze the instituted grounds of unpatentability in accordance with these principles.

B. Prior Art Disclosures

1. Moriarty

Moriarty describes synthesizing treprostinil "via the stereoselective intramolecular Pauson-Khand cyclization." Ex. 1009, 1.[4] Formula 7 of Moriarty is reproduced below:



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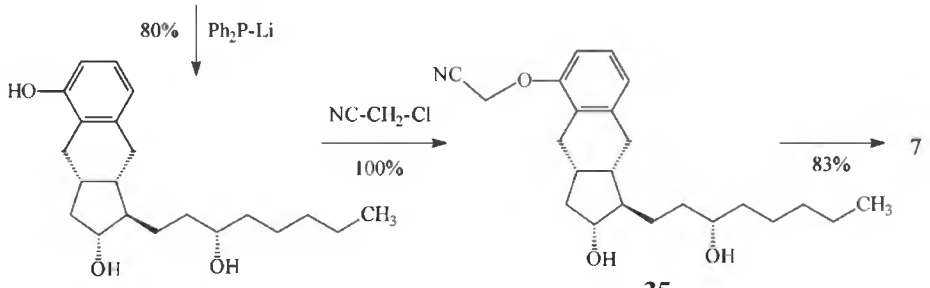
Id. at 3. Formula 7 of Moriarty depicts the chemical structure of treprostinil. *Id.*

An excerpt of Scheme 4 of Moriarty is reproduced below:



34 35

[4] For Moriarty, the parties cite to the pagination added by Petitioner. For consistency, we do the same.

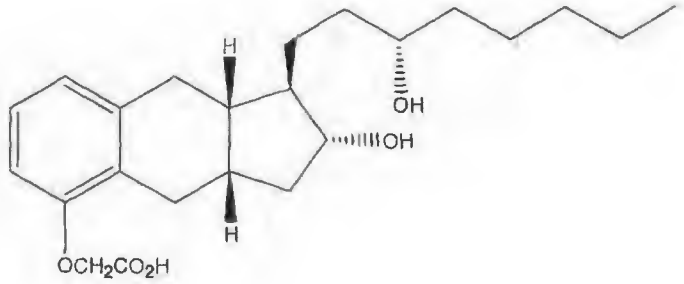
Id. at 6. The excerpted portion of Scheme 4 of Moriarty illustrates that "[t]riol **34** was alkylated at the phenolic hydroxyl group with use of chloroacetonitrile in refluxing acetone with potassium carbonate (**34** → **35**) and nitrile **35** was hydrolyzed with ethanolic potassium hydroxide to yield UT-15 (**7**)," treprostinil. *Id.* at 8.

2. Phares

Phares teaches compounds, including treprostinil and derivatives thereof, "and methods for inducing prostacyclin-like effects in a subject or patient." Ex. 1008, 8.[5] "Treprostinil is a chemically stable analog of prostacyclin, and as such is a potent vasodilator and inhibitor of platelet aggregation." *Id.* Phares states that "[t]he compounds provided herein can be formulated into pharmaceutical formulations and medicaments that are useful in the methods of the invention." *Id.*; *see also id.* at 48 ("provid[ing] for compositions which may be prepared by mixing one or more compounds of the instant invention, or pharmaceutically acceptable salts thereof, with pharmaceutically acceptable carriers, excipients, binders, diluents or the like, to treat or ameliorate a variety of disorders related vasoconstriction and/or platelet aggregation").

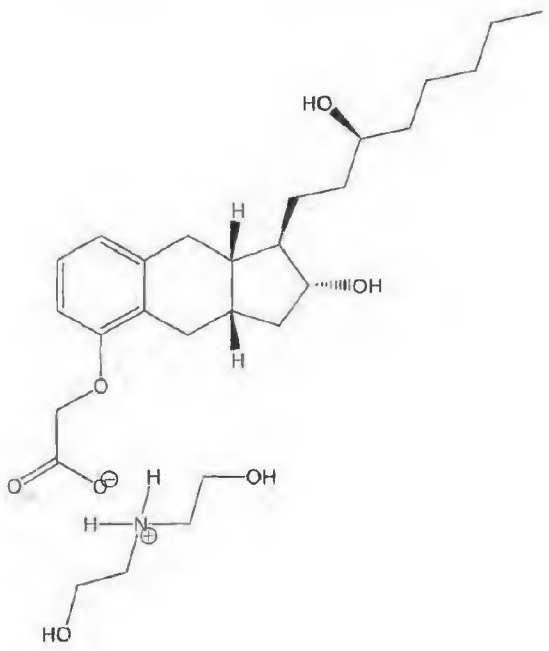
The chemical structure of treprostinil, as shown in Phares, is reproduced below:

[5] For Phares, the parties cite to the original page numbers of the exhibits, and not the pagination added by Petitioner. For consistency, we do the same.



The figure above shows the structure of treprostinil. *Id.* at 8.

Phares teaches that "[a] preferred embodiment of the present invention is the diethanolamine salt of treprostinil." *Id.* at 9. The structure of the diethanolamine salt of treprostinil, as shown in Phares, is reproduced below:

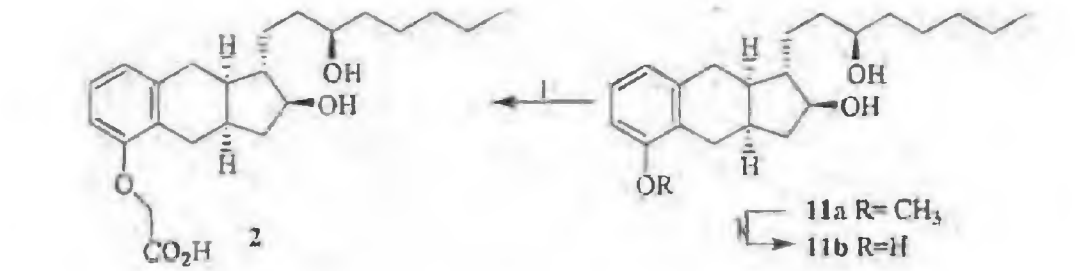


The figure above shows the structure of treprostinil diethanolamine salt. *Id.* at 96 (claim 49).

Phares teaches two crystalline forms of treprostinil diethanolamine salt, the metastable Form A and the thermodynamically more stable Form B.

Id. at 85. Phares states that "[a] particularly preferred embodiment of the present invention is form B of treprostinil diethanolamine." *Id.* at 9.

Phares teaches the synthesis of (-)-treprostinil, the enantiomer of (+)-treprostinil. *Id.* at 39–40. Specifically, Phares teaches the following reaction procedure:



Id. at 40. The figure above shows the reaction procedure for the conversion of 11b to 2. *Id.* Phares describe it as: "(l) i. $ClCH_2CN$, K_2CO_3. ii, KOH, CH_3OH, reflux. 83% (2 steps)." *Id.*

Phares further teaches that "the enantiomer of the commercial drug (+)-treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step and Mitsunobu inversion of the side-chain hydroxyl group." *Id.*, *see also id.* at 39 ("Enantiomers of these compounds . . . can be synthesized using reagents and synthons of enantiomeric chirality of the above reagents.").

C. Claim Construction

In an *inter partes* review, we construe a claim term "using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b)." 37 C.F.R. § 42.100(b). Under that standard, the words of a claim "are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention, i.e.,

as of the effective filing date of the patent application." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312–13 (Fed. Cir. 2005) (en banc).

1. "Pharmaceutical Batch"

In the Petition, Petitioner argues that no construction of claim terms is required and "[a]ll terms should be given their plain and ordinary meaning in the art" at the priority date of the '901 patent. Pet. 18–19. In the Preliminary Response, Patent Owner emphasizes the difference between a "compound," as recited in the claims of the '393 patent, and a "pharmaceutical batch," as recited in challenged claim 1. Paper 6 ("Prelim. Resp."), 8. In proposing the construction for "pharmaceutical batch," Patent Owner relies on the FDA definition of "batch." *Id.* at 9.

In our Decision to Institute, we generally agreed with Patent Owner's proposed construction that

> The POSA viewing the '901 patent claims in light of the '901 patent specification would have understood claim 1's 'pharmaceutical batch' to be a specific quantity of treprostinil (or its salt) that is intended to have uniform character and quality, within specified limits, and is produced according to a single manufacturing order during the same cycle of manufacture, wherein the uniform character and quality is such that it still contains impurities resulting from the method by which it is produced.

Dec. 15–16 (quoting Prelim. Resp. 9). Later, in our Decision Denying Patent Owner's Request on Rehearing of Decision on Institution, we clarified that "we did not construe the term 'pharmaceutical batch' in claim 1 to require storage stability." Paper 14, 6 (citing Dec. 15–16).

In its Reply, Petitioner argues that Patent Owner's construction of "pharmaceutical batch" "pulls language directly from FDA regulations" and

"creates more ambiguity than clarity by introducing terms that themselves would require construction." Reply 4 (internal quotation marks omitted). According to Petitioner, "a POSA would understand 'pharmaceutical batch' to mean one 'made according to the process recited in steps (a)–(d) and optionally (e), wherein no purification steps appear between alkylation and salt formation.'" *Id.* at 5. Petitioner further argues that "under either construction, Moriarty discloses a 'pharmaceutical batch' of 500g." *Id.* at 6.

As discussed below, we agree with Petitioner that the challenged claims exclude any isolation[6] between the alkylation and salt formation steps. *See infra*, Section II.C.3. That interpretation, however, flows from the language "contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil," and not "pharmaceutical batch." *Id.* As a result, we decline to adopt Petitioner's proposed construction of "pharmaceutical batch."

Claim terms need only be construed to the extent necessary to resolve the controversy. *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011). Here, we do not need to define the outer bounds of the term "pharmaceutical batch" because the parties' dispute over this term centers on the issue of storage stability.[7] Patent Owner argues "the correct construction

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[6] The parties use the terms "purification" and "isolation" interchangeably in the papers. We use the term "isolation" in this Decision.

[7] The parties agree on the "pharmaceutical" aspect of the term. We note the '901 patent defines "pharmaceutically acceptable" as "being useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes being useful for veterinary use as well as human pharmaceutical use." Ex. 1001, 5:27–31.

of 'pharmaceutical batch' requires storage stability such that the batch could be stored stably for a period of time customary in pharmaceutical manufacturing." PO Resp. 43 (citing Ex. 2025 ¶ 78)). Petitioner contends otherwise. Reply 6 (arguing Patent Owner's construction "imports storage limitations into 'pharmaceutical batch' (POR9), but the Board's construction did not (Dec. at 15-16)"). We agree with Petitioner.

Patent Owner supports its argument, relying on the testimony of Dr. Pinal, who in turn relies on the definitions of "batch," "in-process material," and "lot" in the FDA regulations. Ex. 2025 ¶ 78 (citing Ex. 2004, 133–34). Even if we consider the FDA regulations, none of the cited definitions mentions, let alone requires, storage. Thus, we reiterate that the term "pharmaceutical batch" in claim 1 does not require storage stability. *See* Paper 14, 6. This determination as to the scope of "pharmaceutical batch" is sufficient for purposes of this Decision, and we need not further address the term.

2. "Storing"/"Storage"

Claim 6 recites "storing a pharmaceutical batch of a salt of treprostinil as claimed in claim 1 at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage." In our Decision to Institute, we agreed with Patent Owner that the terms "storing"/"storage" "require that the stored material possesses stability sufficient to allow manufacture and which maintains integrity for a sufficient period of time to be useful for the preparation of a pharmaceutical product." Dec. 17 (quoting Prelim. Resp. 11).

In its Response, Patent Owner maintains its proposed claim construction. PO Resp. 11. Together with its Response, Patent Owner submitted the Prosecution History of Application No. 13/933,623 ("the '623 application) (Ex. 2028). The '623 application, issued as Patent No. 9,156,786 (the '786 patent), is the parent of the application that issued as the challenged '901 patent. *See* Ex. 1001, code (63); Ex. 2028, 264.

Petitioner asserts that Patent Owner's proposed construction is "inconsistent with its construction of this same term during prosecution of the '901 Patent's parent, the '786 Patent." Reply 7. We agree.

During the prosecution of the '623 application, the applicant amended pending claim 1 as following:

> 1. (Currently Amended) A process for preparing a pharmaceutical product comprising treprostinil or a treprostinil salt, comprising:
>
> combining treprostinil and a base in solution to form a base addition salt;
>
> allowing crystallization of the base addition salt of treprostinil; [[and]]
>
> collecting the base addition salt of treprostinil, storing the collected base addition salt, and preparing a pharmaceutical product comprising treprostinil or a treprostinil salt from the base addition salt after storage.

Ex. 2028, 159. The examiner rejected this claim as obvious over Phares and another prior art reference. *Id.* at 172. The examiner specifically addressed the limitation directed to storing the treprostinil salt. *Id.* at 173–74. According to the examiner,

> The step of storing the treprostinil diethanolamine salt is inherently met by Phares. Examiner is interpreting the term

> "storing" to mean a time period between preparation of treprostinil salt and its use in preparation of a pharmaceutical product. Said limitation is inherently met by Phares. Phares teaches preparation of pharmaceutical products and administration of said compounds to a subject (paragraphs [0049], [0071], [0072], [0074]). It is inherent that some time elapses between preparation of a compound and its use in preparation of a pharmaceutical formulation. Phares describes obtaining an X-ray diffraction spectrum of treprostinil diethanolamine. It is inherent that while obtaining the X-ray diffraction spectrum the compound is being stored.

Id.

In response, the applicant further amended the relevant part of the claim to "storing the collected base addition salt at ambient temperature, and preparing a pharmaceutical product comprising treprostinil or a treprostinil salt from the base addition salt after the storage." *Id.* at 189. Relying on a Rule 132 Declaration of Dr. Liang Guo, the applicant argued:

> [T]he PTO's interpretation of the term "storing" is too broad even under the broadest reasonable interpretation standard. Even under the broadest reasonable interpretation standard, the PTO may not erase the meaning of a step in a method claim that is tied to the preamble. The claim is directed to "preparing a pharmaceutical product." In the accompanying Guo Declaration, Dr. Liang Guo explains that a person of ordinary skill in the art would recognize that the term "stored" in the expression "crude treprostinil salts can be stored as raw material at ambient temperature" in paragraph 0046 of the specification as filed means stored for a period of at least three months. Guo Declaration at ¶ 6. Thus, "storing" in the context of "preparing a pharmaceutical product" would be understood by one of ordinary skill in the art to mean a period of at least three months. Based on this understanding of "storing," Phares clearly does not meet the storing element of claim 1.

Id. at 193; *see also id.* at 198 (Guo Declaration ¶ 6 stating the same). The examiner, apparently finding this argument persuasive, allowed the claims thereafter. *Id.* at 243–44.

"[A]n invention is construed not only in the light of the claims, but also with reference to the file wrapper or prosecution history in the Patent Office." *Graham*, 383 U.S. 1, 33. "The prosecution history of a related patent can be relevant if . . . it addresses a limitation in common with the patent in suit." *Advanced Cardiovascular Sys., Inc. v. Medtronic, Inc.*, 265 F.3d 1294, 1305 (Fed. Cir. 2001); *see also Elkay Mfg. Co. v. Ebco Mfg. Co.*, 192 F.3d 973, 980 (Fed. Cir. 1999) ("When multiple patents derive from the same initial application, the prosecution history regarding a claim limitation in any patent that has issued applies with equal force to subsequently issued patents that contain the same claim limitation.").

Here, the Specification of the '901 patent includes the same language "crude treprostinil salts can be stored as raw material at ambient temperature" addressed in the prosecution of the parent '623 application. Ex. 1001, 17:5–6. More importantly, challenged claim 6 recites the same limitation "preparing a pharmaceutical product . . . after storage" the applicant expressly interpreted there. *See* Ex. 2028, 193. Because "the same claim limitation is at issue, prosecution disclaimer made on the same limitation in an ancestor application will attach," the applicant's interpretation of "storing"/"storage" during the prosecution of the '623 application applies here. *See Omega Eng'g, Inc., v. Raytek Corp.*, 334 F.3d 1314, 1333 (Fed. Cir. 2003).

In the parallel district court case, the court accorded the terms "stored"/"storing"/"storage" their plain and ordinary meaning. Ex. 2035,[8] 1. Under 37 C.F.R. § 42.100(b), we have considered the district court's claim construction. In this case, however, the prosecution history, part of the intrinsic evidence, is so unambiguous that we must apply the applicant's interpretation presented therein. *See Chimie v. PPG Indus., Inc.*, 402 F.3d 1371, 1384 (Fed. Cir. 2005) ("The purpose of consulting the prosecution history in construing a claim is to exclude any interpretation that was disclaimed during prosecution."); *Phillips*, 415 F.3d at 1317.

Petitioner points out that Patent Owner's expert in the parallel district court case, Dr. Robert R. Ruffolo, opined that, in the '901 patent, actual storage was not required.[9] Paper 29, 3–5 (citing Ex. 2034, 130:12–132:4, 132:15–136:11). We acknowledge Dr. Ruffolo's testimony that claim 6 does not require that the pharmaceutical product be made after storage of the pharmaceutical batch of a salt of treprostinil. *See* Ex. 2034, 136:7–11. Claim 6, however, explicitly recites storing a pharmaceutical batch of a salt of treprostinil, and preparing a pharmaceutical product from the pharmaceutical batch after storage. Thus, we discount the cited Ruffolo testimony on "storage" because it "is clearly at odds with the claim construction mandated by the claims themselves." *See Phillips*, 415 F.3d

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[8] The parties agreed to submit the claim construction order from the district court case (Ex. 2035) as supplemental information. Paper 40, 2.

[9] Petitioner asks us to strike "Patent Owner's Submissions Regarding 'Storage'" in Patent Owner Response, Sur-reply, and the two declarations of Dr. Pinal (Exs. 2002, 2025). Paper 29, 8. We address this issue below in Section IV.

at 1318; *see also id.* at 1324 (holding extrinsic evidence cannot be used to "contradict claim meaning that is unambiguous in light of the intrinsic evidence").

In sum, we determine that claim 6 requires actual storage, and in view of the applicant's statements during the prosecution of the parent '623 application, we determine the terms "storing"/"storage" in the context of "preparing a pharmaceutical product" require storing or storage for a period of at least three months.

3. Step (c) of Challenged Claim 1

Step (c) of challenged claim 1 recites "contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil." In its Response, Patent Owner points out that "[t]he claim's preamble requires the pharmaceutical batch be one 'consisting of' what results from the recited steps." PO Resp. 11. According to Patent Owner, "[t]ogether, this language means treprostinil is not isolated from the solution formed in step (b) before forming a salt in step (c)." *Id.* Petitioner does not contest Patent Owner's proposed construction. Reply 3 n.2.

Later, however, Patent Owner retracts its argument, apparently in response to certain disputes between the parties in the co-pending district court case. Sur-reply 8. Relying on the testimony of Dr. Pinal, Patent Owner points out claim 5 of the '066 patent recites "the base is combined with treprostinil that has not been previously isolated." Ex. 2025 ¶ 157 (quoting Ex. 2027, 18:31–33); Sur-reply 8 (citing Ex. 2025 ¶ 157). In contrast, Patent Owner argues "not isolating the treprostinil before contacting it with a base

is ***not*** an explicit limitation of claim 1 of the '901 patent." Sur-reply 8 (quoting Ex. 2025 ¶ 157 (emphasis added by Patent Owner)).

Patent Owner also relies on the testimony of Dr. Ruffolo in the parallel district court case. *Id.* at 8–9 (citing Ex. 2033 ¶ 15; Ex. 2034, 247–48). According to Dr. Ruffolo, "a POSA would understand that the passage in the Patent Owner's Response upon which [Petitioner] Liquidia relies is incorrect to the degree it suggests that Examples 2 and 3 describe synthesizing treprostinil without isolating it prior to salt formation." Ex. 2033 ¶ 15. Patent Owner argues:

> [PO Resp.] at 11 inaccurately suggests that the language of claim 1 means treprostinil is "not isolated" from the solution formed in step (b) before forming a salt in step (c). *See, e.g.*, POR, 15, 29, 34, 53 . . . These statements are unsupported and a POSA would not have understood them as consistent with the claims read in light of the specification.

Sur-reply 8. As a result, Patent Owner states that it "withdraws those statements."[10] *Id.* at 9; *see also* Paper 29, 1.

Whether Patent Owner is allowed to withdraw its arguments regarding step (c) does not have any effect on our construction of step (c). This is because "[w]hen construing claim terms, we first look to, and primarily rely on, the intrinsic evidence, including the claims themselves, the specification, and the prosecution history of the patent, which is usually dispositive."

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[10] Petitioner argues that if Patent Owner is permitted to withdraw the statements related to the issue of "not isolated," then we should strike not only those in Patent Owner Response, as identified by Patent Owner, but also many other statements in the Patent Owner Response, the Pinal Declarations (Exs. 2002, 2025), and the Sur-reply. Paper 29, 1–2. We address this issue below in Section IV.

Sunovion Pharm., Inc. v. Teva Pharm. USA, Inc., 731 F.3d 1271, 1276 (Fed. Cir. 2013). Here, step (c) of challenged claim 1 requires "contacting the solution comprising treprostinil *from step (b)* with a base to form a salt of treprostinil." Ex. 1001, 17:27–29 (emphasis added). The claim language itself, thus, dictates that the solution formed in step (b), and not treprostinil isolated from step (b), is the starting material for forming a salt in step (c).

The Specification of the '901 patent supports our determination. Indeed, the Specification touts that one of the advantages of the disclosed process is that "the treprostinil salts can be synthesized from the solution of treprostinil without isolation," because "[t]he impurities carried over from intermediate steps (i.e. alkylation of triol and hydrolysis of benzindene nitrile) are removed during the carbon treatment and the salt formation step." Ex. 1001, 17:1–11. As a result, we agree with the argument presented in the Patent Owner Response that "claim 1 requires the solution in which treprostinil is formed be used directly in the next salt-forming step without isolating treprostinil in between." *See* PO Resp. 11.

The testimony of Dr. Pinal and Dr. Ruffolo do not change our determination. First, extrinsic evidence in the form of expert testimony, although useful at times, cannot be used to "contradict claim meaning that is unambiguous in light of the intrinsic evidence." *Phillips*, 415 F.3d at 1324. Because the testimony of Patent Owner's experts on this issue are "clearly at odds with the claim construction mandated by the claims themselves," we accord them little weight. *See id.* at 1318.

Second, "extrinsic evidence consisting of expert reports and testimony is generated at the time of and for the purpose of litigation and thus can

suffer from bias that is not present in intrinsic evidence." *Id.* at 1318. Here, Dr. Ruffolo indicated that his testimony was prepared specifically in response to Petitioner's "documentary evidence that treprostinil in [Petitioner] Liquidia's LIQ861 is isolated prior to salt formation and cannot infringe." Ex. 2033 ¶ 4. Thus, the testimony of Dr. Ruffolo on this issue are not sufficiently reliable.

Third, Patent Owner's reliance on claim 5 of the '066 patent is unavailing. Patent Owner argues when it "wants to exclude purification from its claim . . . it knows specifically how to do that." Tr. 56:20–22. Patent Owner essentially invites us to assume that, as an applicant, it always follows the same pattern of claiming. We decline to do so and do not construe step (c) of challenged claim 1 based on the entirely different language in claim 5 of the '066 patent.

In sum, in view of the intrinsic evidence, including the claim language and the Specification, we conclude that treprostinil is not isolated from the solution formed in step (b) before forming a salt in step (c).

D. Level of Ordinary Skill

In the Decision to Institute, we found "the level of ordinary skill in the art is reflected by the prior art, including Phares and Moriarty." Dec. 22. Patent Owner argues that the challenged claims "contemplate batch-scale synthesis and late-stage chemical purification." PO Resp. 23. According to Patent Owner, "scaling up is a separate and difficult process." *Id.* at 24. Thus, Patent Owner contends that an ordinarily skilled artisan "would have been an industrial chemist or chemical engineer with experience in

pharmaceutical manufacturing." *Id.* at 23. We find Patent Owner's definition of the skill level too narrow.

Patent Owner relies on the declaration of Dr. Pinal, who testifies that the '901 patent is "focused on the production of pharmaceutical compositions and products, on a commercial batch-size scale." Ex. 2002 ¶ 91; *see also id.* ¶ 92 (opining that organic and medicinal chemists do not have the "requisite skill set for the large-scale manufacture" of drugs); PO Resp. 24 (arguing an ordinarily skilled artisan is aware of "problems encountered in preparing a commercial-scale pharmaceutical product").

Patent Owner does not explain what "a commercial batch-size scale," a "large-scale," or "a commercial-scale" encompasses. Moreover, during his deposition, Dr. Pinal, Patent Owner's expert, testified that a pharmaceutical product is not limited to a commercial one, and many of them are in clinical trials. Ex. 1018, 111:17–112:8. And during the oral argument, counsel for Patent Owner acknowledged that a compounding pharmacy can also make a pharmaceutical batch. Tr. 47:11–20.

Patent Owner emphasizes the "distinction between the academic and the practical." PO Resp. 24 (citing Ex. 2025 ¶¶ 55–63). Dr. Pinal testifies that "[o]ne cannot overemphasize that benchtop synthetic chemistry is not a viable replacement for, i.e., closely related to, the commercial production of pharmaceutical drug products, which is performed to high scale, in a pilot plant, kilo-lab plant, or manufacturing plant." Ex. 2025 ¶ 55.

Challenged claim 1 requires "the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt." In comparison, Moriarty teaches the synthesis of 441 grams of treprostinil. Ex. 1009, 13. Indeed, treprostinil had

been prepared as described in Moriarty, and used as the active ingredient in Remodulin. Ex. 1001, 1:27–32. And the '901 patent itself describes the Moriarty process as having "[b]atch size: 500 g" with a yield of treprostinil of "~535 g." *Id.* at 15:38, 16:7, 16:60. Yet, Dr. Pinal characterizes Moriaty as on a "benchtop" scale. Ex. 2025 ¶ 92. This inconsistency casts further doubt over Dr. Pinal's testimony on this issue.

We also note that Phares teaches not one, but two, clinical studies with treprostinil diethanolamine. Ex. 1008, 82–86. As Dr. Pinal acknowledged during his deposition, pharmaceutical products include those used in clinical trials, even if they are used only in clinical trials. Ex. 1018, 111:17–112:8. Thus, Phares reflects the skill level, even under Patent Owner's construction.

Patent Owner challenges Dr. Winkler's qualification to provide expert testimony. *See, e.g.*, PO Resp. 23 n.2 ("Prof. Winkler frames the issues in terms of academic and undergraduate lab organic chemistry because that is where his experience lies."); Paper 31,[11] 4 ("Dr. Winkler is unqualified to testify on the relevant subject matter."). We are not persuaded.

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[11] Patent Owner argues that Dr. Winkler does not have qualifications in the relevant field even under Petitioner's own definition of the skill level, as stated in the Declaration of Dr. Hall-Ellis. Paper 31, 4 (citing Ex. 1015 ¶ 16). Dr. Hall-Ellis, in her Declaration in support of the Petition, testified that an ordinarily skilled artisan is "a medical physicist" with "experience in radiation oncology physics." Ex. 1015 ¶ 16. Petitioner later filed a supplemental Hall-Ellis Declaration to correct that error. *See* Ex. 1052.

"A person may not need to be a person of ordinary skill in the art in order to testify as an expert under Rule 702, but rather must be qualified in the pertinent art." Patent Trial and Appeal Board Consolidated Trial Practice Guide[12] 34 ("There is . . . no requirement of a perfect match between the expert's experience and the relevant field."). Here, we are satisfied that Dr. Winkler qualifies as an expert witness "by knowledge, skill, experience, training, or education to testify in the form of an opinion." *See id.*; Ex. 1003.

In sum, after considering the full record developed at trial, we maintain that the level of ordinary skill in the art is reflected by the prior art, including Phares and Moriarty. We further note that our analyses and legal conclusions apply with equal force under the skill level as defined by either party.

E. Obviousness over Phares and Moriarty

Petitioner argues that claims 1–9 of the '901 patent would have been obvious over Moriarty and Phares. Pet. 49–75. After reviewing the entire record, we conclude Petitioner has shown by a preponderance of the evidence that the combination of Moriarty and Phares renders claims 1–5, 8, and 9 obvious. Petitioner, however, has not shown by a preponderance of the evidence that the combination of Moriarty and Phares renders claims 6 and 7 obvious.

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[12] Available at https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf.

1. Claims 1–5, 8, and 9

i. Claim 1

Regarding claim 1, Petitioner points out that Moriarty describes synthesizing treprostinil via the stereoselective intramolecular Pauson-Khand cyclization, and Phares teaches forming treprostinil diethanolamine salt having the same structure as disclosed in the '901 patent. Pet. 53–55 (citing Ex. 1008, 9, 22, 96; Ex. 1009, 1). According to Petitioner, "[t]he combination of Moriarty and Phares discloses the same process steps and product of the '901 patent and as such, the combination of these references would disclose a purity of at least equal purity to that claimed in the '901 patent." *Id.* at 56 (citing Ex. 1002 ¶ 159). In addition, Phares teaches "the pharmaceutical acceptability of the compounds." *Id.* at 29 (citing Ex. 1008, 22). Thus, Petitioner concludes "Moriarty in combination with Phares disclose a pharmaceutical batch consisting of treprostinil or a salt thereof and impurities," as recited in challenged claim 1. *Id.* at 56.

Specifically, Petitioner refers to Moriarty for teaching alkylating benzindene triol 34 to yield nitrile 35, and hydrolyzing nitrile 35 to yield treprostinil. *Id.* at 57, 59 (citing Ex. 1009, 6, 8, 13). Thus, Petitioner contends that Moriarty teaches steps (a) and (b) of challenged claim 1.

Acknowledging that step (c), "the step of reacting treprostinil with a base to form a salt of **7** is not disclosed in Moriarty," Petitioner asserts "this step is clearly disclosed in Phares." *Id.* at 54. Petitioner refers to Phares for teaching dissolving treprostinil in a 1:1 molar ratio mixture of ethanol:water and then adding diethanolamine. *Id.* at 54, 61 (citing Ex. 1008, 22). Petitioner asserts that "a POSA would likely understand the treprostinil acid

disclosed at page 22 [of Phares] to have been isolated before addition of the base." *Id.* at 61 (citing Ex. 1002 ¶ 176). But, according to Petitioner, "not isolating the treprostinil before contacting it with a base is obvious based on what is taught by Phares," and "[a] POSA would be motivated to do so to save a step of isolation." *Id.* (citing Ex. 1002 ¶¶ 177, 178; Ex. 1008; 40).

Petitioner argues that Phares also teaches step (d) because it is needed to form the disclosed crystalline forms of treprostinil diethanolamine salt.[13] *Id.* at 62 (citing Ex. 1008, 85–89).

Regarding the wherein clause reciting "the pharmaceutical batch contains at least 2.9 g of treprostinil or its salt," Moriarty teaches that "[t]he essential requirements for any large-scale, multistep synthesis of a molecule of the complexity of [treprostinil] are very high overall stereoselectivity, high overall chemical yield, and scalability of individual steps to multigram quantities." Ex. 1009, 3. Petitioner refers to Moriarty for synthesizing 441 g of treprostinil. Pet. 63 (citing Ex. 1009, 13).

Petitioner contends that an ordinarily skilled artisan would have had a reason to combine Moriarty and Phares because "Phares is directed to improving treprostinil, and the Moriarty process . . . was a well-known way to make treprostinil." *Id.* at 51–52 (citing Ex. 1002 ¶¶ 148, 151). Petitioner further asserts that an ordinarily skilled artisan would have had a reasonable expectation of success in combining the references because "[t]he proposed combination of Moriarty and Phares yields treprostinil diethanolamine

[13] We do not discuss step (e) because it is an optional step.

salt . . . via the process taught by Phares," and "Phares successfully performed precisely that step." *Id.* at 52–53 (citing Ex. 1002 ¶ 152).

After reviewing the entire record developed at trial, and as explained below, we determine Petitioner has shown, by a preponderance of the evidence, that the combination of Moriarty and Phares teaches each limitation of challenged claim 1. Petitioner has also shown that an ordinarily skilled artisan would have had a reason to combine Moriarty and Phares, and would have had a reasonable expectation of success when doing so.

Patent Owner does not dispute that the combination of Moriarty and Phares teaches steps (a), (b), and (d) of challenged claim 1.[14] Patent Owner also does not dispute that the combined teachings suggest the "at least 2.9 g of treprostinil or its salt" as recited in the wherein clause. Patent Owner, however, challenges Petitioner's accounting of step (c) of claim 1, asserting that "claim 1's recited steps differ from Phares and Moriarty because they do not involve isolation of treprostinil intermediate."[15] PO Resp. 57; *see also id.*

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[14] Patent Owner argues that Phares contains "an insufficient disclosure to provide the POSA with enough conditions to successfully recrystallize [tritreprostinil diethanolamine]." *Id.* at 55. To the extent Patent Owner challenges Phares for not being enabling, this argument is unavailing. "Under § 103 . . . a reference need not be enabled; it qualifies as a prior art, regardless, for whatever is disclosed therein." *Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1357 (Fed. Cir. 2003) (instructing the trial court to reconsider obviousness on remand "without reference to whether [the prior art] is enabled, as enablement of the prior art is not a requirement to prove invalidity under § 103").

[15] Petitioner asks us to strike this and other arguments because Patent Owner seeks to withdraw some statements related to the "no isolation" argument.

at 62 ("[T]he recited steps are different from those disclosed in Moriarty and Phares (no isolation of treprostinil after alkylation and hydrolysis steps before forming a salt)."). Patent Owner also asserts that the product from the combination of Moriarty and Phares does not necessarily include the same impurities as recited in claim 1. *Id.* at 62–64. In addition, Patent Owner contends that Phares and Moriarty are directed to different problems. *Id.* at 54–56. According to Patent Owner, Petitioner "has failed to demonstrate that a POSA would have had the requisite motivation and expectation of success." *Id.* at 58. We address these contentions below.

a. Reason to Combine and Modify

Moriarty teaches synthesis of treprostinil "via the stereoselective intramolecular Pauson-Khand cyclization." Ex. 1009, 1. Similarly, Phares teaches that "the enantiomer of the commercial drug (+)-Treprostinil was synthesized using the stereoselective intramolecular Pauson Khand reaction as a key step." Ex. 1008, 40. Thus, we find that the two references are not directed to problems so different that an ordinarily skilled artisan would not have combined their teachings.

Paper 29, 1–2. We address those requests below in Section IV. Our obviousness analysis, however, remains the same regardless of whether we grant Petitioner's request to strike. This is because, as explained above, based on the intrinsic evidence, we construe claim 1 to exclude isolation between steps (b) and (c). *See supra*, Section II.C.3. Thus, Petitioner must show, with or without Patent Owner's arguments, that the combined teachings of Moriarty and Phares suggest to an ordinarily skilled artisan to skip the intermediate isolation step.

Petitioner asserts that one reason to combine Moriarty and Phares is because "Phares is directed to improving treprostinil, and the Moriarty process . . . was a well-known way to make treprostinil." Pet. 51–52. This assertion is supported not only by the Winkler Declaration (Ex. 1002 ¶ 151), but also by the testimony of Dr. Pinal, Patent Owner's expert. Indeed, Dr. Pinal recognized, "[t]he end of Moriarty is the beginning of Phares." Ex. 1018, 135:6; *see also id.* at 135:16–19 ("Moriarty teaches how to make treprostinil and Phares teaches how to take that treprostinil and further modify it to produce other molecular entities."). As Patent Owner acknowledges, "Phares identifies the diethanolamine salt as a preferred embodiment." PO Resp. 61; Ex. 1008, 9. Thus, we are persuaded that an ordinarily skilled artisan would have had a reason to start with the treprostinil free acid of Moriarty and convert it into the diethanolamine salt.

Phares teaches "treprostinil as the free acid has an absolute oral bioavailability of less than 10%." Ex.1008, 2. According to Patent Owner, this shows "[i]f anything, Phares teaches away from the preparation of treprostinil for use as a pharmaceutical product." PO Resp. 55. We disagree.

As Petitioner argues, an ordinarily skilled artisan would have had a reason to combine Moriarty and Phares because "Phares is directed to improving treprostinil." Pet. 51. One of the improvements is on the bioavailability. *See* Reply 13 (citing Ex. 1017 ¶ 128); Ex. 1008, 83 ("Based on historical intravenous treprostinil sodium data, the mean absolute bioavailability values for the 0.2 mg, 0.5 mg, 1.0 mg and 2.0 mg doses of UT-15C [treprostinil diethanolamine] were estimated to be 21%, 23%, 24% and 25%, respectively.").

Patent Owner contends that, if Petitioner were right that "the claimed invention may have ***worse*** purity than Moriarty and Phares," then "a POSA would have no motivation to change Moriarty at all." PO Resp. 56 (citing Pet. 56; Ex. 2025 ¶ 250). Patent Owner's contention is unavailing.

"[T]he problem motivating the patentee may be only one of many addressed by the patent's subject matter." *KSR*, 550 U.S. at 420; *see In re Kahn*, 441 F.3d 977, 990 (Fed. Cir. 2006) (stating that an ordinarily skilled artisan need not be motivated to combine prior art for the same reason contemplated by the inventor). Here, by taking treprostinil of Moriarty and "further modify[ing] it to produce other molecular entities" (Ex. 1018, 135:16–19), such as treprostinil diethanolamine, Phares, even if it does not improves the purity, improves at least the bioavailability, of treprostinil of Moriarty. *See* Ex. 1008, 2, 83. This provides a sufficient reason for an ordinarily skilled artisan to combine the teachings of Moriarty and Phares.

b. Step (c) and Recited Impurities

Dr. Winkler testifies that, in Phares, "[t]reatment of Compound **11b** with KOH, CH_3OH (methanol) . . . would lead to the formation of a solution of treprostinil carboxylic acid after neutralization." Ex. 1002 ¶ 174. "[I]nstead of isolating the neutral carboxylic acid at this step by removal of the methanol," Dr. Winkler continues, "one could instead add diethanolamine (i.e., a base) to the treprostinil solution so that removal of the methanol would instead leave a salt, specifically, treprostinil diethanolamine salt." *Id.* ¶ 177. According to Dr. Winkler, "[a] POSA would understand that an intermediate purification step is unnecessary because not purifying the intermediate carboxylic acid before addition of a base does not affect salt

formation." *Id.* ¶ 151. Relying on the testimony of Dr. Winkler, Petitioner argues that "a POSA would have sought to combine Moriarty and Phares in order to eliminate the intermediate purification step taught by Moriarty, thereby increasing synthetic efficiency and lowering production costs for treprostinil diethanolamine salt." Pet. 52 (citing Ex. 1002 ¶ 151).

Patent Owner argues that Petitioner "cannot identify support in the asserted art or the background references for these motivations." PO Resp. 61–62. Instead, according to Patent Owner, Petitioner's "proffered motivations—increasing synthetic efficiency and lowering production costs—simply restate two advantages identified in the '901 patent: reducing solvents and labor." *Id.* at 61.

Patent Owner's arguments are unavailing because "there is no requirement that the prior art contain an express suggestion to combine known elements to achieve the claimed invention. Rather, the suggestion to combine may come from the prior art, as filtered through the knowledge of one skilled in the art." *DyStar Textilfarben GmbH & Co. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006). Thus, Petitioner is not required to cite to prior art for expressly disclosing the elimination of the intermediate isolation step.

This is especially true here because "the desire to enhance commercial opportunities by improving a product or process is universal—and even common-sensical." *Id.* at 1368. After all, there is an implicit motivation to combine or to modify prior art teachings when the improvement is technology-independent and the combination or modification "results in a product or process that is more desirable, for example because it is stronger,

cheaper, cleaner, faster, lighter, smaller, more durable, or more efficient." *Id.* Such is the case here. We are persuaded that an ordinarily skilled artisan would have had a reason to eliminate the intermediate isolation step, "thereby increasing synthetic efficiency and lowering production costs for treprostinil diethanolamine salt." Pet. 52; Reply 15; Ex. 1017 ¶¶ 140–144. Thus, we are persuaded that the combination of Moriarty and Phares teaches step (c) of challenged claim 1.

Having decided that an ordinarily skilled artisan would have combined the teachings of Moriarty and Phares, and the combination teaches each required step of challenged claim 1, we turn to Patent Owner's argument that "[a] product from Moriarty and Phares does not inherently include the same resulting impurities." PO Resp. 62. We reject this argument because it is based on an incorrect premise.

Patent Owner contends that "[i]nherency requires identity of steps before inherency can be inferred." *Id.* According to Patent Owner, "the recited steps [of claim 1] are different from those disclosed in Moriarty and Phares." *Id.* In its Response, Patent Owner alleges that in claim 1, there is "no isolation of treprostinil after alkylation and hydrolysis steps before forming a salt." *Id.* Patent Owner later seeks to withdraw this statement (Paper 29, 1) but does not explain what other differences exist between the combined prior art teachings and the required steps of claim 1.

As explained above, we are persuaded by Petitioner's evidence and arguments that the combination of Moriarty and Phares teaches the same process steps as those required in challenged claim 1. Thus, we agree with Petitioner that the product from those steps would include the same resulting

impurities. *See* Pet. 56; Reply 17 (pointing out that claim 1 recites only "impurities *resulting from*" the steps, without identifying any specific "type" of impurity, and without specifying the solvents and reagent required to perform the steps).

c. Reasonable Expectation of Success

Patent Owner also asserts that Petitioner has not shown an ordinarily skilled artisan would eliminate the intermediate isolation step with a reasonable expectation of success.[16] PO Resp. 30–34. Patent Owner argues Petitioner "ignores the practical realities." *Id.* at 30. According to Patent Owner, "a POSA would not know if the proposed step elimination would work," because "in the context of large-scale pharmaceutical manufacturing involving batch production, elimination of an intermediate isolation step has unpredictable impacts on the purity and quality of a final product." *Id.* at 32 (citing Ex. 2025 ¶¶ 158, 289–297), 34 (quotation marks omitted). Patent Owner's arguments are unavailing.

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[16] Under the ground based on Moriarty and Phares, Patent Owner argues that Petitioner "failed to demonstrate a motivation to combine the references to meet the recited claim limitations with a reasonable expectation of success." PO Resp. 52; *see also id.* at 58 (the same). Patent Owner, however, does not provide sufficient analysis to undermine Petitioner's showing of reasonable expectation of success. *See Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (explaining the motivation and reasonable expectation inquiries are different inquiries, and the latter refers to likelihood of success in modifying the prior art to reach the claimed invention). For the sake of completeness, we address here Patent Owner's arguments related to reasonable expectation of success that Patent Owner proffered under the ground based on Phares alone.

Relying on Dr. Winkler's testimony, Petitioner argues "[t]he formation of a carboxylate salt, by the addition of a base to a neutral carboxylic acid, and the subsequent addition of a strong acid to regenerate carboxylic acid, as disclosed in claims 1 and 8 are standard chemistry purification procedures." Pet. 22–23 (citing Ex. 1002 ¶ 47); *see also* Ex. 1002 ¶ 48 (citing Exs. 1010, 1011). "More specifically," according to Petitioner, "contacting a carboxylic acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt, followed by the addition of a strong acid to regenerate the carboxylic acid, was a well-known chemical purification technique in the prior art." Pet. 23–24 (citing Ex. 1002 ¶ 49); *see also* Ex. 1002 ¶ 49 (citing Exs. 1012, 1013).

One of the prior art references Dr. Winkler relies on is Kawakami.[17] *See* Ex. 1002 ¶ 49 (citing Kawakami to support the testimony that "contacting a carboxylic acid of a prostacyclin derivative, such as treprostinil, with a base to form a salt, followed by the addition of a strong acid to regenerate the carboxylic acid, was a well-known chemical purification technique in the prior art"), ¶ 157 (the same); *see also* Pet. 23–24 (citing Ex. 1002 ¶ 49), 55 (citing Ex. 1002 ¶ 157). Kawakami describes using dicyclohexylamine to form a crystalline dicyclohexylamine salt of a methanoprostacyclin derivative, in order to purify the methanoprostacyclin. Ex. 1012, 3. It teaches obtaining a dicyclohexylamine salt by "mixing a methanoprostacyclin derivative [I] . . . with dicyclohexylamine in an appropriate solvent." *Id.* at 5–6. According to

[17] Translation of JP 56-122328, published Sept. 25, 1981 (Ex. 1012).

Kawakami, "[t]he dicyclohexylamine salt of the methanoprostacyclin derivative [I] thus obtained generally has fairly high purity, and the purity can be further improved by recrystallization as needed with the use of an appropriate solvent." *Id.* at 6. Kawakami states "[t]he dicyclohexylamine salt obtained by the present invention can be easily reverted to a free methanoprostacyclin derivative [I] by conventional methods, and the resulting methanoprostacyclin derivative exhibits excellent crystallinity compared with substances not purified according to the present invention." *Id.*

Dr. Winkler testifies that dicyclohexylamine is an amine base with similar reactivity to diethanolamine. Ex. 1002 ¶ 49; Ex. 1017 ¶ 108. Dr. Pinal, Patent Owner's expert, disagrees. Ex. 2025 ¶¶ 180–184. According to Dr. Pinal, even though both dicyclohexylamine and diethanolamine are used as bases to form salts with acidic prostacyclins, they have different miscibilities, which means the salt formation processes using the two bases are "fundamentally different." *Id.*

On this point, we agree with Dr. Winkler that "Dr. Pinal's discussion of the relative miscibilities of dicyclohexylamine and diethanolamine is irrelevant, because both compounds are highly soluble in ethanol and the salt formation in Phares is taught in a 1:1 mixture of water and ethanol." Ex. 1017 ¶ 109. We also agree with Dr. Winkler that "Kawakami teaches the purification of a methanoprostacyclin derivative by salt formation with a secondary amine, which is the same reaction as taught in Phares for the formation of the diethanolamine salt of treprostinil." *Id.*

We also reject Patent Owner's emphasis on "the context of large-scale pharmaceutical manufacturing involving batch production." *See* PO Resp. 32. As explained above, it is unclear what this context means, especially given that Dr. Pinal characterizes 441 grams of treprostinil in Moriarty as on a "benchtop" scale, even though challenged claim 1 recites "2.9 g of treprostinil or its salt." *See supra*, Section II.D.

Regardless, Kawakami recognizes that "establishment of an efficient and *industrially viable method* of separating isomers of methanoprostacyclin derivatives is essential in the development of these derivatives as *pharmaceutical products*." Ex. 1012, 4 (emphases added). It is "[i]n view of" this goal that the Kawakami inventors "succeeded in inventing an extremely simple and *industrially viable purification method*." *Id.* (emphasis added).

Thus, even taking the context of pharmaceutical manufacturing into consideration, we are persuaded that Kawakami "demonstrates that contacting a carboxylic acid of a prostacyclin derivative . . . with a base to form a salt, followed by the addition of a strong acid to regenerate the carboxylic acid, was a well-known chemical purification technique in the prior art." Ex. 1017 ¶ 108. As a result, Petitioner has shown an ordinarily skilled artisan would have had a reasonable expectation of success in eliminating the intermediate isolation step.

d. Conclusion

After reviewing the record, we determine that Petitioner demonstrates by a preponderance of the evidence that the combination of Moriarty and Phares teaches each and every limitation of claim 1, and that an ordinarily

skilled artisan would have had a reason to implement these teachings to arrive at the subject matter of claim 1 with a reasonable expectation of success.

ii. Claims 2–5, 8, and 9

Petitioner provides analysis and citations to record evidence to show Moriarty and Phares teaches or suggests every additional limitation of claims 2–5, 8, and 9. Pet. 64–67, 70–75. Patent Owner does not argue these claims separately. Upon review of Petitioner's arguments and the evidence of record, we adopt Petitioner's mapping of the additional limitations of claims 2–5, 8, and 9 as our own findings.

In sum, we determine that Petitioner has demonstrated by a preponderance of the evidence that the combination of Moriarty and Phares teaches or suggests every additional limitation of claims 2–5, 8, and 9.

iii. Objective Indicia of Non-obviousness

Patent Owner contends that objective indicia demonstrates non-obviousness of the challenged claims. PO Resp. 66–69. We disagree.

Objective indicia of non-obviousness guard against hindsight reasoning in an obviousness analysis, and are often "the most probative and cogent evidence in the record." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1328 (Fed. Cir. 2016). As such, objective indicia of non-obviousness must be considered in every case in which they are presented. *Id.* Objective indicia of non-obviousness include commercial success, long-felt but unsolved needs, failure of others, copying, praise in the art, unexpected results, and industry acceptance. *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1129 (Fed. Cir. 2000).

Patent Owner begins by contending that the '901 patent "contains more than mere argument or conclusory statements; it contains specific data indicating improved properties." PO Resp. 66 (quoting *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995)). Patent Owner follows that assertion by stating that the Specification "identifies a specific need," when it explains that "Treprostinil, and other prostacyclin derivatives are of great importance from a medicinal point of view," and therefore "a need exists for an efficient process to synthesize these compounds on a large scale suitable for commercial production." *Id.* at 67 (quoting Ex. 1001, 1:66–2:3). According to Patent Owner, "[t]his disclosure emphasizes not only the greater benefit for large-scale synthesis but also the higher purity." *Id.* (citing Ex. 1001, 6:4–18). Patent Owner asserts also that the Specification "illustrates these advantages with comparative data," and refers us to other portions of the '901 patent to support that assertion. *Id.* In particular, Patent Owner contends the "storage stability as to the 'pharmaceutical batch' of claim 1 and its dependent claims" is an "unexpected advantage." *Id.* at 68.

We begin by noting, as Petitioner has, that "unexpected advantage" is not a recognized secondary consideration. *See* Pet. Reply 26. Insofar as Patent Owner's argument is considered be one addressing unexpected results, we find Patent's Owner's showing insufficient. As our reviewing court has instructed, to properly evaluate whether a superior property was unexpected, we must first consider what properties were expected. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1371 (Fed. Cir. 2007). To do so, we consider the results of the closest prior art and compare them to those asserted for the claimed invention. *See In re Baxter Travenol Labs.*, 952

F.2d 388, 392 (Fed. Cir. 1991) ("[W]hen unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art."). A showing of unexpected results must be commensurate in scope with the breadth of the claims. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983).

As presented, Patent Owner's arguments are conclusory at best and do not clearly identify what it considers to be the closest prior art or demonstrate how any alleged unexpected results were unexpected compared with the closest prior art. At most, Patent Owner provides a string citation to portions of the Specification and declaration testimony, without providing a discussion of the alleged evidence and explaining how it supports nonobviousness. Nor does Patent Owner demonstrate adequately that the alleged storage stability advantages were commensurate in scope with the breadth of the challenged. And as explained above, the term "pharmaceutical batch" in claim 1 does not require storage stability. *See supra*, Section II.C.1.

In view of the foregoing, we determine that Patent Owner's evidence of objective indicia does not sufficiently demonstrate non-obviousness of claims 1–5, 8, and 9.

iv. Conclusion

Upon review of the record as a whole, including Patent Owner's evidence of objective indicia, and for the reasons discussed above, we determine that Petitioner demonstrates by a preponderance of the evidence that the subject matter of claims 1–5, 8, and 9 would have been obvious over the combination of Moriarty and Phares.

2. Claims 6 and 7

Claim 6 is directed to "[a] method of preparing a pharmaceutical product from a pharmaceutical batch as claimed in claim 1, comprising storing a pharmaceutical batch of a salt of treprostinil as claimed in claim 1 at ambient temperature, and preparing a pharmaceutical product from the pharmaceutical batch after storage." Claim 7 depends from claim 6, and specifies that "the salt of treprostinil is a diethanolamine salt."

Petitioner argues that Phares inherently teaches the limitation of "storing"/"storage." Pet. 68. Petitioner points out that Phares teaches two crystalline forms of treprostinil diethanolamine salt, Form A and Form B. *Id.* (citing Ex. 1008, 85–89). According to Petitioner,

> Phares further discloses that Form B is made from Form A, with full conversion to Form B at ambient temperature after 7 days, 15°C after 11 days and 30°C after 1 day, suggesting stability of the treprostinil diethanolamine salt at these temperatures . . . . A POSA would . . . understand that full conversion after 7 days at ambient temperature, as disclosed by Phares, inherently teaches that Form B is stable at ambient temperature and therefore could be stored at ambient temperature.

Id. (internal citations omitted).

Patent Owner contends that Petitioner confuses "***relative*** thermodynamic stabilities with actual stability." PO Resp. 50. According to Patent Owner, "Phares provides no stability data for Form B. That one polymorph is more stable than another does not show that either is stable enough for storage in a pharmaceutical batch." *Id.* at 50–51. We agree.

Phares teaches two crystalline forms of treprostinil diethanolamine salt, Form A and Form B. Ex. 1008, 85. Phares states that Form B appears to be "thermodynamically more stable" than the "metastable" Form A. *Id.*

at 85, 89. Phares reaches this conclusion after performing inter-conversion experiments in two different solvents, using Forms A and B material. *Id.* at 89. In isopropanol, Phares reports full conversion from Form A to Form B at ambient temperature after seven days. *Id.* Dr. Winkler testifies that this "inherently teaches that Form B is stable at ambient temperature and therefore could be stored at ambient temperature." Ex. 1002 ¶ 203. Dr. Winkler, however, does not provide a sufficient explanation or cite any support for this conclusory statement.

Petitioner argues that "Phares discloses synthesis and isolation of treprostinil diethanolamine without specifying a temperature." Reply 19 (citing Ex. 1008, 22). According to Dr. Winkler, "[b]ecause there is no temperature limitation here, a POSA would understand that treprostinil diethanolamine was being isolated at ambient temperature, so that it was stable at ambient temperature." Ex. 1017 ¶ 150 (citing Ex. 2029, 249). Petitioner also argues that the fact "Phares mentions no special storage conditions for the treprostinil diethanolamine salt" further suggests nothing other than ambient temperature is required. Reply 20 (citing Ex. 1017 ¶ 153).

We are not persuaded by Dr. Winkler's testimony or Petitioner's arguments. As discussed above, we determine claim 6 requires actual storage, and the terms "storing"/"storage" require storing or storage for a period of at least three months. *See supra*, Section II.C.2. Even if an ordinarily skilled artisan would have understood that treprostinil diethanolamine is stable so that it can be isolated at ambient temperature, nothing in Phares suggests the salt would be stable for at least three months.

Petitioner contends the '901 patent refers to "storing" in a single sentence: "Additional advantages of this process are: (a) crude treprostinil salts can be stored as raw material at ambient temperature . . . ."[18] Reply 20 (citing Ex. 1001, 17:4–6). According to Petitioner, this "confirms that a POSA would understand that all crude treprostinil salts can be stored at ambient temperature." *Id.* "Applying the same knowledge," Petitioner continues, "a POSA would understand the treprostinil diethanolamine salt described [in Phares] to be storable at room temperature." *Id.* (citing Ex. 1017 ¶ 155). We are not persuaded.

An invention "must be viewed not with the blueprint drawn by the inventor, but in the state of the art that existed at the time." *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985). We cannot use the disclosure of the '901 patent as an instruction manual or template to supply the missing "storing"/"storage" limitation in order to piece together an obviousness theory. *See In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992).

Petitioner does not argue, let alone point to any persuasive evidence of the record to show, an ordinarily skilled artisan would have understood Phares to teach storing treprostinil diethanolamine for at least three months. Thus, we conclude Petitioner has not demonstrated by a preponderance of the evidence that the subject matter of claims 6 and 7 would have been obvious over the combination of Moriarty and Phares.

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[18] Elsewhere, Petitioner argues that "the '901 patent does not sufficiently describe or enable this limitation of claim 6." Pet. 68. We do not address § 112 issues in an *inter partes* review.

F. Obviousness over Phares

Petitioner argues that claims 1–9 of the '901 patent would have been obvious over Phares. Pet. 26–48.

Because we determine that Petitioner demonstrates by a preponderance of the evidence that the subject matter of claims 1–5, 8, and 9 would have been obvious over the combination of Moriarty and Phares (*see supra*, Section II.E.1), we do not address the challenge of those claims here. *See SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348, 1359 (2018) (holding a petitioner "is entitled to a final written decision addressing all of the claims it has challenged"); *Boston Sci. Scimed, Inc. v. Cook Grp. Inc.*, 809 F. App'x 984, 990 (Fed. Cir. Apr. 30, 2020) (non-precedential) (recognizing that the "Board need not address issues that are not necessary to the resolution of the proceeding" and, thus, agreeing that the Board has "discretion to decline to decide additional instituted grounds once the petitioner has prevailed on all its challenged claims").

For claims 6 and 7, Petitioner presents the same arguments and evidence here as under the ground based on the combination of Moriarty and Phares. *Compare* Pet. 43–45, *with id.* at 68–70; *see also* Reply 26 (relying on the same arguments regarding "storing"/"storage" for both challenges). For the same reason explained above, we reject those arguments. *See supra*, Section II.E.2. Thus, we conclude Petitioner has not demonstrated by a preponderance of the evidence that the subject matter of claims 6 and 7 would have been obvious over Phares.

III. CONSTITUTIONAL CHALLENGE

Patent Owner contends subjecting the '901 patent to *inter partes* review violates its constitutional rights. PO Resp. 69–71. Patent Owner's arguments on this issue are foreclosed by the decisions in *Celgene Corp. v. Peter*, 931 F.3d 1342, 1362–63 (Fed. Cir. 2019) and *United States v. Arthrex, Inc.*, 141 S. Ct. 1970, 1986–87, 1997 (2021). As such, we do not further consider or address Patent Owner's arguments.

IV. PETITIONER'S REQUEST TO STRIKE

Petitioner seeks to strike portions of Patent Owner's Response, Sur-reply, and the Pinal Declarations (Exs. 2002, 2025). Paper 29; Exs. 1043–1046.

Petitioner's first request, related to the "not isolated" arguments, is unusual because it is prompted by Patent Owner's requested withdrawal of its own arguments. *See* Ex. 3001. We explained the situation above. *See supra*, Section II.C.3. Briefly, in its Response, Patent Owner argues "treprostinil is not isolated from the solution formed in step (b) before forming a salt in step (c)." PO Resp. 11. Later, in its Sur-reply, Patent Owner attempts to withdraw certain statements related to "not isolated" in the Response. Sur-reply 8–9; Paper 29, 1. Petitioner objected, asking us to deny this request. Ex. 3001; Tr. 16:3–5. Alternatively, Petitioner seeks to strike Patent Owner's proposed construction of step (c) in the Response and "strike all arguments in the Patent Owner Response, expert declarations (Exhibits 2002, 2025), and Sur-Reply relying on the POR's proposed construction." Ex. 3001; Tr. 16:5–9; Paper 29, 1–2; Exs. 1043–1046.

As explained above, we determine that, in claim 1, treprostinil is not isolated from the solution formed in step (b) before forming a salt in step (c). *See supra*, Section II.C.3. Because our construction is dictated by the intrinsic evidence, and not by Patent Owner' arguments, we dismiss Patent Owner's request to withdraw its statements related to "not isolated" as moot.

Petitioner asks us to strike, in addition to the language Patent Owner seeks to withdraw, large portions of Patent Owner's Response, together with portions of Patent Owner's Response and expert declarations, because they allegedly rely on the language Patent Owner seeks to withdraw. Ex. 3001; Tr. 16:5–9; Paper 29, 1–2; Exs. 1043–1046. We deny this request.

In the Petition, Petitioner argues that an ordinarily skilled artisan "would likely understand the treprostinil acid disclosed at page 22 [of Phares] to have been isolated before addition of the base." Pet. 61. Petitioner, however, asserts that "not isolating the treprostinil before contacting it with a base is obvious based on what is taught by Phares." *Id.* In other words, Petitioner implicitly construed claim 1 to exclude an isolation step between steps (b) and (c). *See* Tr. 14:6–16:2 (maintaining that excluding isolation "is the actual right construction"). Patent Owner, thus, is entitled to respond to Petitioner's arguments on this issue, regardless of its own position on how the claim should be construed.

More importantly, we construe claim 1 to exclude isolation between steps (b) and (c). Thus, Petitioner must demonstrate the asserted prior art and the knowledge in the field teach or suggest the elimination of the isolation step, and an ordinarily skilled artisan would have had a reason to eliminate the isolation step, and would have had a reasonable expectation of success

when doing so. Petitioner cannot circumvent these requirements by striking Patent Owner's arguments challenging, albeit unsuccessfully, Petitioner's showing.

Petitioner also asks us to strike Patent Owner's "Submissions Regarding 'Storage'" in the Patent Owner Response, Sur-reply, and the two declarations of Dr. Pinal (Exs. 2002, 2025). Paper 29, 8. According to Petitioner, Patent Owner's expert in the parallel district court case, Dr. Robert R. Ruffolo, testified that, in the '901 patent, actual storage was not required. *Id.* at 3–5 (citing Ex. 2034, 130:12–132:4, 132:15–136:11). This is inconsistent, Petitioner asserts, with Patent Owner's position in this proceeding. *Id.* at 2. Even though Petitioner is correct on this point, we decline to strike Patent Owner's arguments related to "storage."

As explained above, we determine claim 6, by explicitly reciting "storing," requires actual storage. *See supra*, Section II.C.2. An expert's testimony, clearly at odds with the unambiguous claim language, does not absolve Petitioner of its burden to demonstrate that the prior art teaches or suggests this limitation.

In sum, in view of our construction of step (c) and the terms "storing"/"storage" based on the intrinsic evidence, we deny Petitioner's Request to Strike.

V. PATENT OWNER'S MOTION TO EXCLUDE

Patent Owner filed a Motion to Exclude Exhibits 1002 and 1012, as well as the portions of the Petition and Reply that rely on these exhibits. Paper 31, 2. For the reasons provided below, we deny Patent Owner's Motion to Exclude.

A. Winkler Declaration (Ex. 1002)

Petitioner relies on the Winkler Declaration (Ex. 1002) to support the arguments in the Petition. Pet. 3. Patent Owner contends that Exhibit 1002 "purports to be a declaration, but without authentication because it lacks the statutorily-required oath or caveat for a declaration." Paper 31, 3 (citing 35 U.S.C. § 25; 37 C.F.R. § 42.2). Alternatively, Patent Owner asserts that "Prof. Winkler's declaration warrants no weight because it lacks the required oath or perjury statement." PO Resp. 17 (citing 35 U.S.C. § 25(b); 37 C.F.R. § 42.63).

Under our Rules, "[e]vidence consists of affidavits, transcripts of depositions, documents, and things" (37 C.F.R. § 42.63(a)), and "[u]ncompelled direct testimony must be submitted in the form of an affidavit" (*id.* § 42.53(a)). "*Affidavit* means affidavit or declaration under [37 C.F.R.] §1.68 . . . . [A] declaration under 28 U.S.C. 1746 may be used as an affidavit." *Id.* § 42.2.

As Patent Owner correctly points out, Exhibit 1002, the purported declaration of Dr. Winkler, "does not state that the testimony is true or believed to be true, much less reference the penalty for making willful false statements." PO Resp. 18.

Petitioner does not dispute this deficiency. Instead, Petitioner argues that Patent Owner "waived its argument regarding Dr. Winkler's declaration under 37 C.F.R. § 42.63, because it did not timely object to the issue with sufficient particularity . . . to allow correction in the form of supplemental evidence." Paper 32, 1 (internal quotation marks omitted). We disagree with Petitioner.

First, "[a]ny objection to evidence submitted during a preliminary proceeding must be filed within ten business days of the institution of the trial." 37 C.F.R. § 42.64(b)(1). We instituted trial on October 13, 2020; and Patent Owner timely filed and served its objections to Exhibit 1002 on October 27, 2020. *See* Paper 10.

Second, "[a] motion to exclude evidence must be filed to preserve any objection." 37 U.S.C. § 42.64(c). Patent Owner timely filed a Motion to Exclude Exhibit 1002 (Paper 31, 2), and thus, has properly preserved its objections to Exhibit 1002.

Third, Petitioner faults Patent Owner for, in the objections, "generically restat[ing] FRE 802, 901, and 902, and never identified the oath as the issue." Paper 32, 1; *see also* Tr. 21:19 ("The objections weren't specific to the perjury statement."); *id.* at 23:2–4 (arguing that Patent Owner's objection was "ambiguous"). We disagree.

Patent Owner objected to Exhibit 1002 "under FRE 901-902 as lacking authentication and not self-authenticating because it lacks sufficient indicia that the exhibit is what it purports to be." Paper 10, 3. According to Patent Owner, Petitioner "does not state that it did not understand the objection . . ., that it sought clarification from [Patent Owner], or that it could not identify how the exhibit lacked authentication." Paper 37, 1.

During oral argument, Petitioner explained that "we didn't realize that it was the perjury statement in particular that they were referring to. Or, we didn't realize that it had been omitted. And so, we looked at the signature and saw that it was there." Tr. 22:1–4; *see also id.* at 23:3–6 ("[W]hen we saw a lack of authentication [objection], we thought, oh, did Dr. Winkler not

sign his declaration. We saw that it was signed. We did not realize that they were actually referring to the perjury statement.").

Counsel for Patent Owner pointed out, and Petitioner did not dispute, "if it's a declaration, the only thing that would render it inauthentic would be the lack of a signature or an oath[; those] are the only two things it could possibly be." Tr. 40:3–5. We find Patent Owner's objection sufficient to put Petitioner on notice that the authentication of Exhibit 1002 is problematic; no more is required of Patent Owner. The fact that Petitioner did not realize the authentication objection is directed to the lack of perjury statement, instead of the lack of a signature, does not make Patent Owner's objection ambiguous. Thus, we conclude that Patent Owner has not waived its argument regarding Dr. Winkler's declaration under 37 C.F.R. § 42.63.

Petitioner argues that "any omissions in Dr. Winkler's declaration with respect to the oath or perjury statement were harmless and have been cured." Paper 32, 2; Reply 1–2. Petitioner points out that (1) Patent Owner deposed Dr. Winkler on his opinions in Exhibit 1002; and (2) Dr. Winkler "refiled Ex. 1002 as Ex. 1039" and Patent Owner "has not moved to exclude Ex. 1039 or any [of] Dr. Winkler's opinions therein." Paper 32, 2; Reply 2. According to Petitioner, Patent Owner "is exalting form over substance in renewing this objection." Paper 32, 2. We reject Petitioner's cavalier attitude towards this matter.

First, because Exhibit 1039 was filed without proper authorization, we give it no weight in rendering this Decision. Exhibit 1039 is not a declaration in support of the Reply; instead, it was a "[r]efiled Declaration of Jeffrey D. Winkler, Ph.D. (Ex. 1002)" that is in support of the Petition.

Paper 42, 4; Ex. 1039, cover page. But, the Petition was filed on March 30, 2020 (Pet. 76; Paper 3, 1), and Exhibit 1039 was filed on March 1, 2021 (Ex. 1039, 81). Petitioner does not explain how a declaration executed eleven months after can support the Petition.

Exhibit 1039 is not proper supplemental evidence either. Under 37 C.F.R. § 42.64(b)(2), "[t]he party relying on evidence to which an objection is timely served may respond to the objection by serving supplemental evidence within ten business days of service of the objection." During oral argument, counsel for Patent Owner represented, and counsel for Petitioner did not dispute, that Petitioner served Exhibit 1039 on the same day it filed the Reply. Tr. 39:5–23. That is more than four months after Patent Owner timely served the objections to Exhibit 1002. Thus, Exhibit 1039 is not proper supplemental evidence in response to Patent Owner's objection. *See* Paper 31, 2 ("No supplemental evidence was timely filed to address the[] objections.").

Second, Petitioner relies on *Google LLC v. CyWee Group Ltd.*, IPR2018-01257, Paper 69 (PTAB Sept. 6, 2019), and *Fidelity Information Services, LLC v. Mirror Imaging, LLC*, CBM2017-00064, Paper 54 (January 2, 2019). Paper 32, 2. As Petitioner recognizes, in those two cases, the Board "grant[ed] party *authorization to correct* unsworn declaration when opposing party cross-examined the expert." *Id.* (emphasis added). What is critically missing here, however, is that Petitioner never sought leave to correct the unsworn declaration. In fact, Petitioner never brought the issue to the attention of the Board. Instead, it resorted to self-help and "fixed" the issue through a filing without authorization. *See* Tr. 22:5–7.

Despite our concerns over Petitioner first submitting a defective "declaration," and then disregarding our Rules when attempting to correct the mistake, we find Patent Owner has suffered no undue prejudice. As Petitioner emphasizes, Patent Owner deposed Dr. Winkler on his opinions in Exhibit 1002. Paper 32, 2 (citing Ex. 2026). Indeed, Patent Owner's counsel conceded so during the oral argument. Tr. 64:5–6 ("I'd be hard pressed to sit here and say . . . that we suffered a specific cognizable prejudice."). As a result, we deny Patent Owner's Motion to Exclude Exhibit 1002.

B. Kawakami (Ex. 1012)

Patent Owner also seeks to exclude Kawakami because, although it purports to be a translation of JP56-122328, it is not authenticated, and not a verified translation. Paper 31, 2, 10–11.

Patent Owner points out that Exhibit 1012 "contains neither the purported Japanese document being translated, nor a verified translator's declaration." *Id.* at 10. Patent Owner states that it "timely objected to EX1012 under FRE 402, 403, 802, 803-807, 901, 902, 1001-1003, 1012," but Petitioner failed to timely serve any supplemental evidence to address these objections. *Id.* at 3 (citing Paper 10, 2–3). Patent Owner also contends that Petitioner has failed to comply with 37 C.F.R. § 42.63(b). *Id.* at 11; *see also* 37 C.F.R. § 42.63(b) (requiring the party who relies on a document in a foreign language to file, with the original document, an English translation, and an affidavit attesting to the accuracy of the translation).

Petitioner argues "Ex. 1012 is exactly the same Kawakami document that was submitted in the IPR2016-00006 as Ex. 1007." Paper 32, 7. Together with its Opposition to Patent Owner's Motion to Exclude,

Petitioner submitted Exhibits 1047–1051, which are "the original Japanese version of Kawakami and declarations attesting to and confirming the accuracy of the translation," originally filed as Exhibits 1006, 1007, 1011, 1019, and 1020 in IPR2016-00006. *Id.* at 8. According to Petitioner, "[t]he filing of these exhibits remedies any failure to comply with § 42.63(b) or FRE 902(3), which in any event is harmless error."

As with Petitioner's omission and later self-help relating to Exhibit 1002, we do not condone Petitioner's omission and self-help here either. Petitioner contends that Patent Owner "did not move to exclude the identical Kawakami translation in IPR2016-00006, and the Board [in that case] relied on the same translation for an entire ground in its final written decision." Paper 32, 7. Petitioner fails to recognize that the petitioner in that case properly complied with our Rules, and there was no good-faith basis for Patent Owner to seek any exclusion.

Despite our disappointment over Petitioner's repeated carelessness, we deny Patent Owner's Motion to Exclude Exhibit 1012. First, Petitioner relies on Exhibit 1012 through Dr. Winkler's testimony. Pet. 23–24 (citing Ex. 1002 ¶ 49), 55 (citing Ex. 1002 ¶ 157). Under Federal Rules of Evidence 703, Dr. Winkler may rely on facts or data that are not admissible themselves.

Second, "a comparison between the IPR copies of a reference and a version of the reference proven to be prior art was evidence that the IPR reference was prior art." *Valve Corp. v. Ironburg Inventions Ltd.*, 8 F.4th 1364, 1371 (Fed. Cir. 2021) (citing *VidStream LLC v. Twitter*, Inc., 981 F.3d 1060, 1066–67 (Fed. Cir. 2020)). In the '393 Decision, the panel

relied on Kawakami in analyzing one of the obviousness grounds. *See* the '393 Dec. 68–84. Kawakami was properly authenticated in that proceeding. *See* IPR2016-00006, Exs. 1006, 1007, 1011, 1019, 1020. Because a comparison shows Exhibit 1012 in this case is the same as Exhibit 1007 in IPR2016-00006, we deny Patent Owner's Motion to Exclude Exhibit 1012.

VI. PETITIONER'S MOTION TO SUBMIT SUPPLEMENTAL INFORMATION

Under our Rules,

> A party seeking to submit supplemental information more than one month after the date the trial is instituted, must request authorization to file a motion to submit the information. The motion to submit supplemental information must show why the supplemental information reasonably could not have been obtained earlier, and that consideration of the supplemental information would be in the interests-of-justice.

37 C.F.R. § 42.123(b).

With our authorization, Petitioner filed a Motion, seeking to submit the Claim Construction Order from the parallel district court case. Paper 38, 1. At the time of the Motion, only the Proposed Order was available. Ex. 1054. Patent Owner does not oppose the Motion in this respect, and submitted the official Order as Exhibit 2035. Paper 40, 2. Patent Owner represents that Petitioner consented to this submission. *Id.*

Our Rules require that we consider "[a]ny prior claim construction determination concerning a term of the claim in a civil action . . . that is timely made of record in the *inter partes* review proceeding." 37 C.F.R. § 42.100(b). The parties timely filed the Claim Construction Order before

the oral hearing in this proceeding. *See* Paper 38, 2–3 (arguing the *Markman* Order could not have been obtained earlier). Thus, Petitioner's Motion to submit the Claim Construction Order from the district court case is granted, and Exhibit 2035 is admitted into evidence in this proceeding.[19]

Petitioner also seeks to submit the transcript from the *Markman* hearing at the district court (Ex. 1054). Paper 38, 1. According to Petitioner, "the hearing transcript contains further evidence of Patent Owner's inconsistencies in its claim construction positions between the tribunals, and the district court's evaluation of those inconsistencies as likely disclaimer." *Id.* at 5; *see also id.* at 6–8 (listing "relevant excerpts").

Patent Owner opposes the Motion in this respect. Paper 40, 2. According to Patent Owner, many of Petitioner's citations to the hearing transcript "amount to attempts to supplement the record with its own further attorney argument and engage in a game of gotcha regarding allegedly inconsistent statements." *Id.* at 2–3.

Because we consider the Claim Construction Order from the district court, and because the *Markman* hearing transcript helps to explain how the district court came to its constructions in the Order, we find it is in the interests of justice to admit the hearing transcript into evidence of the record in this proceeding, for just that purpose.

In sum, Petitioner's Motion to Submit Supplemental Information is granted.

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[19] Because Exhibit 1054 is superseded, we expunge it from the record.

VII. CONCLUSION[20]

After reviewing the entire record and weighing evidence offered by both parties, we determine that (1) Petitioner has demonstrated by a preponderance of the evidence that claims 1–5, 8, and 9 of the '901 patent would have been obvious over the combination of Moriarty and Phares; and (2) Petitioner has not demonstrated by a preponderance of the evidence that claims 6 and 7 of the '901 patent would have been obvious over either Phares alone, or the combination of Moriarty and Phares.

In summary:

Claims	35 U.S.C. §	Reference(s)	Claims Shown Unpatentable	Claims Not shown Unpatentable
1–9	103	Moriarty, Phares	1–5, 8, 9	6, 7
1–9	103	Phares		6, 7
Overall Outcome			1–5, 8, 9	6, 7

[20] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this decision, we draw Patent Owner's attention to the April 2019 *Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding. See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. § 42.8(a)(3), (b)(2).

VIII. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has demonstrated by a preponderance of the evidence that claims 1–5, 8, and 9 are unpatentable;

FURTHER ORDERED that Petitioner has not demonstrated by a preponderance of the evidence that claims 6 and 7 are unpatentable;

FURTHER ORDERED that Petitioner's Request to Strike (Paper 29) is denied;

FURTHER ORDERED that Patent Owner's Motion to Exclude (Paper 31) is denied;

FURTHER ORDERED that Petitioner's Motion to Submit Supplemental Information (Paper 38) is granted; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2020-00770
Patent 9,604,901 B2

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EXHIBIT 6

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

UNITED THERAPEUTICS CORPORATION,	)	
Plaintiff,	)	
v.	)	C.A. No. 20-755 (RGA) (JLH)
LIQUIDIA TECHNOLOGIES, INC.,	)	
Defendant.	)	

STIPULATION OF PARTIAL JUDGMENT OF NON-INFRINGEMENT

WHEREAS, the Court has construed the term "contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil" in claims 1 and 8 of U.S. Patent No. 9,604,901 (the "'901 patent") to mean "contacting the solution comprising treprostinil from step (b) with a base to form a salt of treprostinil, wherein the salt is formed without isolation of treprostinil after alkylation and hydrolysis" (D.I. 245);

WHEREAS, Plaintiff has preserved its argument for a different construction of that term;

WHEREAS, based on the discovery in the litigation Plaintiff does not contend that Defendant's current product infringes the '901 patent under the Court's construction of that term;

WHEREAS, to simplify the proceedings and facilitate appellate review of the Court's claim construction, Plaintiff agrees to the ministerial step of the entry of judgment of noninfringement as to the '901 patent under the Court's construction of that term, while preserving its appellate rights;

NOW, THEREFORE, based on the Court's construction of that term, Plaintiff hereby stipulates and agrees to the entry of a partial judgment reflecting the Court's claim construction, as follows:

Judgment of Non-Infringement of U.S. Patent No. 9,604,901 is entered for Defendant and against Plaintiff on Counts 3 and 4 of the First Amended Complaint (D.I. 16);

Plaintiff expressly reserves and does not waive its ability to challenge the Court's claim-construction ruling on appeal, and therefore to challenge the above disposition of Counts 3 and 4 and Counterclaim IV on appeal.

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December 28, 2021

IT IS SO ORDERED on this 3rd day of Jan, 2022.

J.

CERTIFICATE OF SERVICE

I hereby certify that on December 28, 2021, I caused the foregoing to be electronically filed with the Clerk of the Court using CM/ECF, which will send notification of such filing to all registered participants.

I further certify that I caused copies of the foregoing document to be served on December 28, 2021, upon the following in the manner indicated:

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EXHIBIT 7

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Paper 78
Entered: July 19, 2022

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

LIQUIDIA TECHNOLOGIES, INC.,
Petitioner,

v.

UNITED THERAPEUTICS CORPORATION,
Patent Owner.

IPR2021-00406
Patent 10,716,793 B2

Before ERICA A. FRANKLIN, CHRISTOPHER M. KAISER, and DAVID COTTA, *Administrative Patent Judges.*

KAISER, *Administrative Patent Judge.*

JUDGMENT
Final Written Decision
Determining All Challenged Claims Unpatentable
35 U.S.C. § 318(a)

INTRODUCTION

A. Background

Liquidia Technologies, Inc. ("Petitioner") filed a Petition (Paper 2, "Pet.") requesting an *inter partes* review of claims 1–8 of U.S. Patent No. 10,716,793 B2 (Ex. 1001, "the '793 patent"). United Therapeutics Corporation ("Patent Owner") filed a Preliminary Response. Paper 13 ("Prelim. Resp.").

On August 11, 2021, we instituted *inter partes* review of claims 1–8 of the '793 patent on all grounds set forth in the Petition. Paper 18 ("Inst. Dec."). After institution of trial, Patent Owner filed a Response (Paper 29, "PO Resp."), Petitioner filed a Reply (Paper 44), and Patent Owner filed a Sur-Reply (Paper 55). In addition, both parties filed Motions to Exclude Evidence (Papers 65 and 66), Oppositions to their respective opponents' Motions to Exclude (Papers 68 and 69), and Replies in support of their own Motions to Exclude (Papers 71 and 72). At the request of both parties, we held an oral hearing, the transcript of which has been entered into the record. Paper 77 ("Tr.").

We have jurisdiction under 35 U.S.C. § 6. This is a Final Written Decision under 35 U.S.C. § 318(a) as to the patentability of the challenged claims of the '793 patent. For the reasons discussed below, we determine Petitioner has established by a preponderance of the evidence that each of claims 1–8 of the '793 patent is unpatentable.

B. Related Matters

The parties identify *United Therapeutics Corporation v. Liquidia Technologies, Inc.*, 1:20-cv-00755-RGA (D. Del.) ("the District Court proceeding"), as a related matter. Pet. 1; Paper 3, 1.

C. The Asserted Grounds of Unpatentability

Petitioner contends that claims 1–8 of the '793 patent are unpatentable based on the following grounds (Pet. 30–68):[1]

Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
1–8	103(a)	'212 patent,[3] Voswinckel JESC,[4] Voswinckel JAHA[5]
1–8	103(a)	'212 patent, Voswinckel JESC
1	102(a)	Ghofrani[6]
1, 3, 8	103(a)	Voswinckel JAHA, Ghofrani
1, 3	102(a)	Voswinckel 2006[7]

[1] Petitioner also relies on declarations from Nicholas Hill, M.D., and Igor Gonda, Ph.D. Exs. 1002, 1004, 1106, 1107.

[2] The '793 patent claims a priority date of May 15, 2006, and Petitioner "assumes the relevant priority date . . . is May 15, 2006." Pet. 12; Ex. 1001, code (60). Accordingly, patentability is governed by the versions of 35 U.S.C. §§ 102 and 103 preceding the amendments in the Leahy-Smith America Invents Act ("AIA"), Pub. L. No. 112–29, 125 Stat. 284 (2011).

[3] US 6,521,212 B1, issued Feb. 18, 2003 (Ex. 1006) (alleged to be prior art under 35 U.S.C. §§ 102(a), (b), (e)).

[4] Voswinckel, R., et al., *Inhaled treprostinil is a potent pulmonary vasodilator in severe pulmonary hypertension*, 25 EUROPEAN HEART J. 22 (2004) (Ex. 1007) (alleged to be prior art under 35 U.S.C. § 102(b)).

[5] Robert Voswinckel, et al., *Inhaled Treprostinil Sodium (TRE) For the Treatment of Pulmonary Hypertension*, in Abstracts from the 2004 Scientific Sessions of the American Heart Association, 110 CIRCULATION III-295 (Oct. 26, 2004) (Ex. 1008) (alleged to be prior art under 35 U.S.C. § 102(b)).

[6] Hossein Ardeschir Ghofrani, et al., *Neue Therapieoptionen in der Behandlung der pulmonalarteriellen Hypertonie*, 30 HERZ 296–302 (June 2005) (Ex. 1010) (alleged to be prior art under 35 U.S.C. § 102(a)). We rely on the English translation that follows the German original article as part of Ex. 1010.

[7] Robert Voswinckel, et al., *Inhaled Treprostinil for Treatment of Chronic Pulmonary Arterial Hypertension*, 144 ANNALS OF INTERNAL MEDICINE

Claim(s) Challenged	35 U.S.C. §[2]	Reference(s)/Basis
2, 4–8	103(a)	Voswinckel 2006, '212 patent

D. The '793 Patent

The '793 patent, titled "Treprostinil Administration by Inhalation," issued on July 21, 2020. Ex. 1001, codes (45), (54). The patent "relates to methods and kits for therapeutic treatment and, more particularly, to therapeutic methods involving administering treprostinil using a metered dose inhaler and related kits." *Id.* at 1:20–23.

Treprostinil "is a prostacyclin analogue" that may be used to treat pulmonary hypertension. *Id.* at 5:37–41. According to the '793 patent, it was previously known to administer treprostinil by intravenous, subcutaneous, or inhalation routes to treat any of several conditions, including pulmonary hypertension. *Id.* at 5:42–58.

The '793 patent relates to the administration of treprostinil in high concentrations over a short inhalation time. *Id.* at 16:61–63, 17:44–46. This method of administration is described as reducing pulmonary vascular resistance and pulmonary artery pressure, as well as increasing cardiac output. *Id.* at 16:32–42, Fig. 10.

E. Illustrative Claim

Claims 1–8 of the '793 patent are challenged. Claim 1 is independent and illustrative; it recites:

> 1. A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a

149–50 (January 2006) (Ex. 1009) (alleged to be prior art under 35 U.S.C. § 102(a)).

> formulation comprising treprostinil or a pharmaceutically acceptable salt thereof with an inhalation device, wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof delivered in 1 to 3 breaths.

Ex. 1001, 18:23–31.

ANALYSIS

A. Claim Construction

In an *inter partes* review, we construe a claim in an unexpired patent "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." 37 C.F.R. § 42.100(b) (2020). "[T]he ordinary and customary meaning of a claim term is the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (en banc). "Importantly, the person of ordinary skill in the art is deemed to read the claim term not only in the context of the particular claim in which the disputed term appears, but in the context of the entire patent, including the specification." *Id.*

Neither party presents any terms for construction. Pet. 12–13 ("Petitioner does not believe construction of any claim term is required"); PO Resp. 7 (not proposing construction of any terms). Accordingly, we determine that no express construction of any claim term is necessary in order to decide whether to institute trial. *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) (citing *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)

("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.")).

B. Asserted Obviousness over '212 Patent, Voswinckel JESC, and Voswinckel JAHA

Petitioner argues that claims 1–8 would have been obvious over the combination of the '212 patent, Voswinckel JESC, and Voswinckel JAHA. Pet. 30–46. Patent Owner argues that Petitioner fails to show that Voswinckel JESC and Voswinckel JAHA are prior art to the '793 patent. PO Resp. 11–18. Patent Owner also argues that Petitioner fails to show that this combination of references teaches or suggest all the limitations of any of the challenged claims. PO Resp. 18–22, 38–40. In addition, Patent Owner also argues that Petitioner fails to show that a person of ordinary skill in the art would have had a reason to combine the teachings of these references. *Id.* at 23–38.

1. '212 Patent

The '212 patent teaches "[a] method of delivering benzindene prostaglandins to a patient by inhalation." Ex. 1006, code (57). In particular, the '212 patent teaches the use of "[a] benzindene prostaglandin known as UT-15," which "has unexpectedly superior results when administered by inhalation compared to parenterally administered UT-15 in sheep with induced pulmonary hypertension." *Id.* There is evidence in the present record that "UT-15" was also known as "Remodulin" or "treprostinil sodium." Ex. 1035, 582. According to the '212 patent, the UT-15 may be delivered either as droplets formed "from a solution or liquid containing the active ingredient(s)" via a nebulizer, or as a solid-phase powder via an inhaler. Ex. 1006, 5:30–41.

According to the '212 patent, this method may be used to "treat[] pulmonary hypertension in a mammal." *Id.* at 14:9–12. Moreover, the '212 patent teaches "medical use" of its method in a "human." *Id.* at 7:4–5. The necessary dose to achieve "a particular therapeutic purpose will, of course, depend upon the specific circumstances of the patient being treated and the magnitude of the effect desired by the patient's doctor. Titration to effect may be used to determine proper dosage." *Id.* at 6:66–7:3. "[A]erosolized UT-15 has a greater potency as compared to intravascularly administered UT-15," so the '212 patent teaches delivering "only a fraction (10–50%) of the dosage delivered intravascularly" when using its inhalation delivery method. *Id.* at 8:8–12. Even at "high doses," however, the '212 patent teaches a lack of "significant non-lung effects, i.e., heart rate, cardiac output." *Id.* at 10:51–54.

2. Voswinckel JESC

Voswinckel JESC discusses a study to investigate "the acute hemodynamic response to inhaled treprostinil." Ex. 1007, 7. Of the 29 patients in the study, eight were administered a placebo, groups of six patients each were administered 16, 32, and 48 μg/mL solutions of treprostinil, and three patients were administered a solution containing 64 μg/mL of treprostinil. *Id.* Each administration used an "OptiNeb ultrasound nebulizer, [made by] Nebu-Tec, Germany" for six minutes. *Id.* For each patient, various measurements were taken before administration of the treprostinil and at 0, 15, 30, 60, 90, 120, 150, and 180 minutes after administration. *Id.* According to Voswinckel JESC, "[t]reprostinil inhalation results in a significant long-lasting pulmonary vasodilatation,"

and, "at a concentration of 16 μg/mL, near maximal pulmonary vasodilatation is achieved without adverse effects." *Id.*

3. Voswinckel JAHA

Voswinckel JAHA discusses a study of 17 patients with "severe pulmonary hypertension" who received treprostinil inhalations. Ex. 1008, 3. These inhalations each involved "3 single breaths" using a "pulsed OptiNeb® ultrasound nebulizer" and a "600 μg/mL" treprostinil solution. *Id.* In addition, "[t]wo patients with idiopathic PAH received compassionate treatment with 4 inhalations of TRE per day after the acute test" and were "treated for more than 3 months." *Id.* According to Voswinckel JAHA, "inhalation resulted in a sustained, highly pulmonary selective vasodilatation over 120 minutes," showing "strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing," and "[t]olerability is excellent even at high drug concentrations and short inhalation times (3 breaths)." *Id.*

4. Prior-Art Status of Voswinckel JESC and Voswinckel JAHA

In arguing that claims 1–8 would have been obvious, Petitioner relies on Voswinckel JESC and Voswinckel JAHA, but Patent Owner argues that Petitioner fails to show sufficiently that either of these references qualifies as a "printed publication." PO Resp. 11–18.

Only "prior art consisting of patents or printed publications" may form "the basis of" an *inter partes* review. 35 U.S.C. § 311(b). Neither Voswinckel JESC nor Voswinckel JAHA is a patent, so Petitioner may not rely on these references unless they are "printed publications." *Id.* Public accessibility is the "touchstone in determining whether a reference constitutes a printed publication," and a reference is considered publicly

accessible only if it was "disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *Kyocera Wireless Corp. v. Int'l Trade Comm'n*, 545 F.3d 1340, 1350 (Fed. Cir. 2008) (quoting *SRI Int'l, Inc. v. Internet Sec. Sys. Inc.*, 511 F.3d 1186, 1194 (Fed. Cir. 2008); *In re Hall*, 781 F.2d 897, 898–99 (Fed. Cir. 1986)).

Patent Owner argues that, because Petitioner relies on Voswinckel JESC and Voswinckel JAHA having been "stored in libraries, public accessibility requires that the reference be both available at the library and sufficiently indexed or catalogued by the priority date." PO Resp. 12 (citing *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1348 (Fed. Cir. 2016); *In re Klopfenstein*, 380 F.3d 1345, 1349 (Fed. Cir. 2004)). According to Patent Owner, Petitioner fails to show sufficiently either of these requirements. *Id.* at 12–18.

But Petitioner does not rely solely on availability in libraries to show the prior-art status of Voswinckel JESC and Voswinckel JAHA. Instead, Petitioner also argues that "Voswinckel JESC is an abstract presented at the European Society of Cardiology (JESC) Congress," that Voswinckel JAHA "was publicly presented at the 2004 Scientific Sessions of the American Heart Association," and that both references were cited in other documents dating from before the priority date of the '793 patent whose public accessibility is not at issue. Pet. 22; Reply 3–4, 6–8.

Patent Owner objects that Petitioner's public-presentation and citation-in-other-references arguments are untimely because they should have been, but were not, presented in the Petition. Sur-Reply 2–3. We disagree. First, the argument that Voswinckel JESC was presented publicly

appears in the Petition. Pet. 22. Second, although other of Petitioner's arguments appear for the first time in the Reply, they are not untimely. Reply 3–4, 6–8.

Petitioner is permitted a "limited opportunit[y]" to present new evidence in or with its Reply, as long as that new evidence is "responsive to the prior briefing" and does not constitute "changing theories after filing [the] petition." *Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29, at 14–15 (PTAB Dec. 20, 2019) (precedential). Here, both of the arguments that Patent Owner alleges are new—the argument that Voswinckel JESC and Voswinckel JAHA were presented publicly and the argument that these references were cited in other publicly available references—respond to Patent Owner's argument in the Patent Owner Response that Voswinckel JESC and Voswinckel JAHA were not publicly accessible. PO Resp. 11–18. The argument that Voswinckel JESC was publicly presented is not a change in theory from the Petition, because Petitioner presented this argument in the Petition. Pet. 22. As to both Voswinckel JESC and Voswinckel JAHA, Petitioner's Reply evidence showing citation to the references in other publicly accessible documents is merely additional evidence supporting Petitioner's original theory that a person of ordinary skill in the art could have located the references. Accordingly, we find that the following arguments made by Petitioner are not untimely: (1) that Voswinckel JESC was presented publicly, (2) that Voswinckel JESC was referenced in a publicly accessible document, and (3) that Voswinckel JAHA was referenced in a publicly accessible document.

Given the evidence supporting Petitioner's timely arguments, we are persuaded that Petitioner has shown by a preponderance of the evidence that

Voswinckel JESC and Voswinckel JAHA were publicly accessible. "[T]he presence of a 'research aid' can . . . establish public accessibility" of a reference if that research aid "provide[s] a skilled artisan with a sufficiently definite roadmap leading to" the reference by "provid[ing] enough details [to] determine that an interested party is reasonably certain to arrive at the destination: the potentially invalidating reference." *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1350 (Fed. Cir. 2016).

Here, Petitioner directs us to research aids for finding both Voswinckel JESC and Voswinckel JAHA: a "June 2005 Ghofrani article in the journal *Herz*" for the former, and "a March 2005 article authored by Roxana Sulica et al. in the *Expert Review of Cardiovascular Therapy*" for the latter. Reply 3, 7 (citing Ex. 1010, 298, 301; Ex. 1104, 359). The Ghofrani article cites Voswinckel JESC as providing a solution to patients experiencing "pain at the injection site" by replacing injected treprostinil for "pulmonary arterial hypertension" with "*inhaled* treprostinil." Ex. 1010, 298 (citing reference 6), 301 (defining reference 6 as Voswinckel JESC). The Ghofrani article also discusses the study reported in Voswinckel JESC, summarizing both the "major reduction in pulmonary selective pressure and resistance" and the lack of "adverse effects" described in Voswinckel JESC. *Id.* The Sulica article cites to Voswinckel JAHA, explaining that the reference reports that "inhaled treprostinil demonstrated substantial pulmonary vasodilatory efficacy in acute administration, as well as symptomatic and functional benefit in chronic use in a small number of PAH patients." Ex. 1104, 351, 359. Thus, both the Ghofrani article and the Sulica article provide roadmaps directing a person of ordinary skill in the art looking for successful studies discussing the use of inhaled treprostinil in

pulmonary arterial hypertension straight to Voswinckel JESC or Voswinckel JAHA. Because these articles provide these roadmaps, they are "research aid[s]" that "establish [the] public accessibility" of Voswinckel JESC and Voswinckel JAHA. *Blue Calypso*, 815 F.3d at 1350.

5. Analysis

Petitioner argues that the combination of the '212 patent, Voswinckel JESC, and Voswinckel JAHA teaches or suggests the subject matter of claims 1–8 and that a person of ordinary skill in the art would have had a reason to combine the teachings of these references with a reasonable expectation of success. Pet. 30–46. Patent Owner argues that this combination of references fails to teach or suggest delivering a dose of treprostinil within the dose range of the challenged claims in a single dosing event of one to three breaths. Prelim. Resp. 42–55.

a. Claim 1

(1) "A method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof"

Claim 1 recites "[a] method of treating pulmonary hypertension comprising administering by inhalation to a human suffering from pulmonary hypertension a therapeutically effective single event dose of a formulation comprising treprostinil or a pharmaceutically acceptable salt thereof." Ex. 1001, 18:23–27. Petitioner argues that the '212 patent, Voswinckel JESC, and Voswinckel JAHA each teach or suggest this limitation. Pet. 35–37. Patent Owner does not dispute this argument. PO Resp. 10–40.

The '212 patent teaches treating pulmonary hypertension via inhalation of a benzindene prostaglandin called UT-15, which was also known as "treprostinil sodium." Ex. 1006, code (57) (identifying "benzindene prostaglandin" as "UT-15"), 2:66–3:5 ("This invention relates to . . . a method of treating pulmonary hypertension by administering an effective amount of a benzindene prostaglandin to a mammal in need thereof by inhalation."); Ex. 1035, 582 ("UT-15" also known as "treprostinil sodium"). Voswinckel JAHA teaches treating "patients with severe pulmonary hypertension" with "Inhaled Treprostinil Sodium (TRE)" with "3 single breaths" of "TRE solution 600 μg/ml," resulting in "strong pulmonary selective vasodilatory efficacy with a long duration of effect following single acute dosing." Ex. 1008, 3. Voswinckel JESC describes "the acute hemodynamic response to inhaled treprostinil" following the administration to patients of nebulized treprostinil solution in concentrations of 16, 32, 48, and 64 μg/ml for six minutes, resulting in "significant long-lasting pulmonary vasodilatation" without "adverse effects." Ex. 1007, 7.

Accordingly, Petitioner has shown by a preponderance of the evidence that the '212 patent, Voswinckel JESC, and Voswinckel JAHA each teach or suggest this portion of claim 1.

(2) "With an inhalation device"

Next, claim 1 recites "with an inhalation device." Ex. 1001, 18:27–28. Petitioner argues that the '212 patent, Voswinckel JESC, and Voswinckel JAHA each teach or suggest this limitation. Pet. 37. Patent Owner does not dispute this argument. PO Resp. 10–40. The '212 patent teaches the use in its inhalation method of "a nebulizer, inhaler, atomizer or aerosolizer" to "form[] droplets from a solution or liquid containing the

active ingredient(s)." Ex. 1006, 5:30–32. Both Voswinckel JESC and Voswinckel JAHA teach the use of a "nebulizer" in their inhalation methods. Ex. 1007, 7 ("OptiNeb ultrasound nebulizer"); Ex. 1008, 3 ("the pulsed OptiNeb® ultrasound nebulizer"). Dr. Hill testifies that a person of ordinary skill in the art would have understood "that nebulizers and inhalers are inhalation devices." Ex. 1002 ¶ 94. Accordingly, Petitioner has shown by a preponderance of the evidence that the '212 patent, Voswinckel JESC, and Voswinckel JAHA each teach or suggest this limitation of claim 1.

(3) "Wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof"

Claim 1 recites "wherein the therapeutically effective single event dose comprises from 15 micrograms to 90 micrograms of treprostinil or a pharmaceutically acceptable salt thereof." Ex. 1001, 18:28–30. Petitioner argues that the combination of the '212 patent and Voswinckel JESC teaches or suggests this limitation. Pet. 37–40. Patent Owner disagrees. PO Resp. 18–38.

Petitioner calculates the dose that the prior art teaches delivering by inhalation in three separate ways: (1) relying on Voswinckel JESC's solution concentrations and solution volumes taught by Ex. 1037, (2) relying on Voswinckel JESC's solution concentrations and solution volumes normally delivered according to the testimony of Petitioner's declarants, and (3) relying on the '212 patent's conversion from an intravascular treprostinil dose to an equivalent inhaled dose. Pet. 22–24, 38–39. According to Petitioner, each of these three calculation methods results in a teaching of a

therapeutically effective single event dose comprising from 15 micrograms to 90 micrograms of treprostinil. *Id.*

We agree with Patent Owner that Petitioner's first and third calculation methods do not demonstrate that the prior art taught or suggested a therapeutically effective single event dose comprising from 15 micrograms to 90 micrograms of treprostinil, and we do not discuss these calculations any further. The preponderance of the evidence, however, supports Petitioner's argument that its second calculation demonstrates that the prior art taught or suggested a therapeutically effective single event dose comprising from 15 micrograms to 90 micrograms of treprostinil.

Voswinckel JESC teaches that "patients inhaled solvent solution (placebo) (n=8) or treprostinil for 6 min (OptiNeb ultrasound nebulizer, Nebu-tec, Germany) in concentrations of 16, 32, 48, and 64 μg/ml (n=6, 6, 6, and 3 patients)." Ex. 1007, 7. Although this teaching shows administration to patients of inhaled solutions with particular concentrations of treprostinil, it does not disclose the amount of solution administered, which is necessary in order to calculate the amount of treprostinil administered. *Id.* Petitioner directs us to the testimony of its declarants, Dr. Nicholas Hill and Dr. Igor Gonda, to understand how a person of ordinary skill in the art would have interpreted Voswinckel JESC's disclosure. Pet. 23 (citing Ex. 1002 ¶ 65; Ex. 1004 ¶ 56). Dr. Gonda testifies that "in May 2006 . . . nebulizers conventionally deliver[ed] between 1 and 5 mL" of solution. Ex. 1004 ¶ 56. Relying on Dr. Gonda's testimony as well as his own experience, Dr. Hill testifies that a person of ordinary skill in the art in 2006 would have understood that "nebulizers . . . nebulize (i.e. aerosolize liquid) at least" 1 mL of solution. Ex. 1002 ¶ 65.

Multiplying Voswinckel JESC's 16, 32, 48, or 64 micrograms of treprostinil per milliliter of solution by the 1 to 5 milliliters of solution in the testimony of Drs. Hill and Gonda, a person of ordinary skill in the art would have interpreted Voswinckel JESC as teaching the delivery of 16–80, 32–160, 48–240, or 64–320 micrograms of treprostinil. Each of those four dose ranges has at least one endpoint that falls within the 15–90 microgram claimed range.

Patent Owner argues that this evidence is insufficient to show that the combination of the '212 patent, Voswinckel JESC, and Voswinckel JAHA teaches or suggests a therapeutically effective single event dose comprising from 15 micrograms to 90 micrograms of treprostinil. Specifically, Patent Owner argues that the volume of solution that Drs. Hill and Gonda testify was typically used in nebulizers is "the fill volume," or the amount of solution loaded into a nebulizer to be nebulized, which cannot be used with the concentrations in Voswinckel JESC to arrive at the amount of treprostinil actually delivered to a patient. PO Resp. 30–31. This is because "there is no guarantee that the entire fill volume would be completely nebulized in" the time period over which Voswinckel JESC teaches delivering its dose of treprostinil. *Id.* at 30. In addition, Patent Owner argues that there were other factors that might have caused less than all the solution nebulized by a nebulizer to be actually delivered to the patient, none of which Petitioner accounts for. *Id.* at 31–32.

Petitioner "presented evidence that nebulizers at the time typically involved fill volumes of 1-5mL." Reply 10–11. To the extent that something less than the entire fill volume was delivered to the patient, either because it was not nebulized or because other factors resulted in the

nebulized solution not reaching the mouthpiece, the preponderance of the evidence still supports the actual delivered solution volume being at least one milliliter. Dr. Hill testifies that the "at least 1 mL" of solution he discusses is the volume that "nebulizers at the time were known to nebulize," not the amount of liquid loaded into the nebulizer. Ex. 1002 ¶ 65. Patent Owner's declarant, Dr. Aaron Waxman, testifies that standard nebulizers had fill volumes of "3 to 5 [milliliters]" and that he had never administered a dose as low as one milliliter to a patient. Ex. 1108, 153:1–22; 156:12–16.

Thus, Voswinckel JESC teaches delivering solution with a treprostinil concentration of 16, 32, 48, or 64 micrograms per milliliter, and the preponderance of the evidence supports a finding that a person of ordinary skill in the art would have understood the volume of solution delivered in Voswinckel JESC to be at least one milliliter. Accordingly, Petitioner has shown by a preponderance of the evidence that Voswinckel JESC teaches or suggests a therapeutically effective single event dose comprising from 15 micrograms to 90 micrograms of treprostinil.

(4) "Delivered in 1 to 3 breaths"

Claim 1 recites "delivered in 1 to 3 breaths." Ex. 1001, 18:31. Petitioner argues that Voswinckel JAHA teaches or suggests this limitation. Pet. 40–41. Patent Owner does not dispute this teaching of Voswinckel JAHA. PO Resp. 10–40.

Voswinckel JAHA teaches delivering to patients "a TRE inhalation by use of the pulsed OptiNeb® ultrasound nebulizer (3 single breaths, TRE solution 600 µg/ml)." Ex. 1008, 3. It also reports that "[t]olerability is excellent even at high drug concentrations and short inhalation times (3

breaths)." *Id.* Accordingly, Petitioner has shown by a preponderance of the evidence that Voswinckel JAHA teaches or suggests this limitation of claim 1.

b. Reason to Combine with a Reasonable Expectation of Success

As discussed above, Petitioner has shown sufficiently on the present record that the combination of the '212 patent, Voswinckel JESC, and Voswinckel JAHA teaches or suggests every limitation of claim 1. This alone is not sufficient to show that the challenged claims would have been obvious; Petitioner also must show that a person of ordinary skill would have had a reason to combine the teachings of the references and would have had a reasonable expectation of success in doing so.

Petitioner argues that a person of ordinary skill in the art would have had a reason to combine the teachings of the '212 patent, Voswinckel JESC, and Voswinckel JAHA. Pet. 30–34. Patent Owner argues that a person of ordinary skill in the art would have had "serious concerns about side effects" that would have persuaded them not to combine the teachings of the '212 patent, Voswinckel JESC, and Voswinckel JAHA. PO Resp. 37–38.

The '212 patent teaches the use of inhaled treprostinil sodium for the treatment of pulmonary hypertension at doses between 10 and 50 percent of the doses needed for intravascular delivery. Ex. 1006, code (57), 6:1–2, 8:8–12. According to the '212 patent, the inhaled treprostinil sodium is used in sheep, which are a model for pulmonary hypertension in humans. *Id.* at 9:14–27. Dr. Hill testifies that, based on these teachings, a person of ordinary skill in the art would have looked for further information regarding "experimentation [with] inhaled treprostinil in humans." Ex. 1002 ¶ 78. On

the present record, such information can be found in Voswinckel JESC, which reports on a study in which humans with pulmonary hypertension inhaled treprostinil and experienced "significant long-lasting pulmonary vasodilatation . . . without adverse effects." Ex. 1007, 7.

Dr. Hill testifies that, based on the teachings of these references a person of ordinary skill would reasonably have expected that treprostinil could safely and effectively treat pulmonary hypertension in humans. Ex. 1002 ¶ 79. Dr. Hill also testifies that a person of ordinary skill in the art "would have been motivated to further decrease the 6 minute administration time in Voswinckel JESC." Ex. 1002 ¶ 80. Specifically, Dr. Hill testifies that patients often did not adhere to "inhalation therapy for respiratory diseases," that "[p]oor adherence to medication was known to correlate with worse outcomes," and that "reducing administration time or the number of breaths required for therapy [was known to] improve adherence rates." *Id.* (citing Ex. 1002 ¶¶ 36–37; Ex. 1030, 63; Ex. 1032, 179–80; Ex. 1077, 4). Voswinckel JAHA teaches administering treprostinil in three breaths using a high concentration of treprostinil in the aerosolized solution. Ex. 1008, 3. Accordingly, Dr. Hill testifies that a person of ordinary skill in the art would have looked to Voswinckel JAHA to improve patient adherence to the treatment suggested by the combination of the '212 patent and Voswinckel JESC, providing a reason to combine its teachings with those of the other two references. Ex. 1002 ¶¶ 80–82.

Against this evidence, Patent Owner directs us to the report in Voswinckel JESC that "there were no significant adverse effects" at the lowest treprostinil concentration but that "mild and transient" "[h]eadache, cough or bronchoconstriction were observed" in some patients at higher

doses, and that one patient at Voswinckel JESC's highest treprostinil dose "complained of major headache for 1 hour." Ex. 1007, 7; *see* PO Resp. 37–38. As Patent Owner puts it, "Voswinckel JESC warns in its Conclusion that 'at a concentration of 16 μg/ml, near maximal pulmonary vasodilation is achieved without adverse effects' but '[a]t higher doses, local and systemic side effects may occur.'" PO Resp. 37–38 (quoting Ex. 1007, 7). Because Petitioner's proffered reason to combine the teachings of the '212 patent, Voswinckel JESC, and Voswinckel JAHA requires an increase in treprostinil concentration in order to administer the full dose in three breaths, Patent Owner argues that Voswinckel JESC's warning about side effects at higher doses would have persuaded a person of ordinary skill in the art not to pursue such a course. *Id.*

The preponderance of the evidence supports Petitioner's position. Patent Owner is correct that Voswinckel JESC notes that side effects could occur more frequently at higher doses than at lower doses. Ex. 1007, 7. But there is considerable evidence of record that a person of ordinary skill in the art would not have avoided increasing Voswinckel JESC's dose due to the side effects reported in Voswinckel JESC. First, Dr. Hill testifies that "[p]otential side effects are always weighed against potential clinical benefit, and pulmonary arterial hypertension is a serious, life-threatening disease where physicians and patients are more willing to tolerate side effects . . . to obtain clinical benefit." Ex. 1106 ¶ 74. Second, Dr. Waxman testifies that "[u]sually the headache goes away" and "there are things that can be done to help ameliorate the cough so in general we are able to get over that issue." Ex. 1108, 101:19–102:10. Together with Voswinckel JESC's description of potential side effects as "mild and transient," this evidence supports a

finding that a person of ordinary skill in the art would not have been deterred from pursuing the course that is supported by the evidence to which Petitioner directs us.

With respect to reasonable expectation of success, Petitioner argues that a person of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of the '212 patent, Voswinckel JESC, and Voswinckel JAHA because Voswinckel JAHA teaches that "[t]olerability is excellent" for its short-duration, high-concentration treprostinil inhalation therapy. Pet. 33 (citing Ex. 1008, 3). Other than the argument discussed above about side effects reported in Voswinckel JESC, Patent Owner does not raise any timely counter to this argument.[8] PO Resp. 10–40. The record supports Petitioner's argument. Ex. 1008, 3.

Accordingly, Petitioner has shown by a preponderance of the evidence that a person of ordinary skill in the art would have had a reason to combine the teachings of the '212 patent, Voswinckel JESC, and Voswinckel JAHA and that they reasonably would have expected to succeed in doing so.

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[8] In the Sur-Reply, Patent Owner raises for the first time three arguments against a reasonable expectation of success. Sur-Reply 21–22 (arguing that a person of ordinary skill in the art would not expect success in delivering Voswinckel JESC's dose over Voswinckel JAHA's three breaths because (1) it would require "increas[ing] the number [of] doses per day," (2) Voswinckel JAHA "lacked any placebo arm," and (3) Voswinckel JESC and Voswinckel JAHA used patients with differing pulmonary vascular resistances). "A sur-reply may only respond to arguments raised in the corresponding reply." 37 C.F.R. § 42.23(b). Petitioner's Reply did not raise any argument regarding a reasonable expectation of success. Reply 1–27. Therefore, we do not consider these newly raised arguments as they exceed the proper scope of the Sur-Reply.

c. Objective Indicia of Nonobviousness

Patent Owner directs us to evidence of three objective indicia that Patent Owner argues show the nonobviousness of the challenged claims. PO Resp. 55–62. Petitioner argues that the claims would have been obvious despite the evidence to which Patent Owner directs us. Reply 23–27.

(1) Unexpected Results

First, Patent Owner directs us to evidence that allegedly demonstrates that the challenged claims would have been nonobvious because they "unexpectedly achieved a therapeutically effective dose that was well tolerated" despite the fact that such "high doses of treprostinil were known in the art to produce dose-limiting side effects." PO Resp. 55. According to Patent Owner, the challenged claims "produce[d] a new and unexpected result which is different in kind and not merely in degree from the results of the prior art," which is evidence of those claims' nonobviousness. *Id.* at 55–57 (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)). Specifically, Patent Owner argues that the inhaled treprostinil dose recited in the challenged claims represented an increase of "an order of magnitude" over "the maximal tolerated dose" of "intravenous epoprostenol" or "intravenous treprostinil." *Id.* at 56. Similarly, Patent Owner argues that the challenged claims cover doses of inhaled treprostinil higher than a dose of inhaled iloprost that many patients were unable to tolerate. *Id.* at 56–57.

"[U]nexpected results must establish . . . a difference between the results obtained and those of the closest prior art." *Bristol-Myers Squibb v. Teva Pharms. USA*, 752 F.3d 967, 977 (Fed. Cir. 2014). Petitioner argues that the prior art over which Patent Owner argues the challenged claims showed unexpected results is not the closest prior art. Reply 24. We agree.

As noted above, Patent Owner argues that the challenged claims show unexpected results over inhaled iloprost, intravenous epoprostenol, and intravenous treprostinil. PO Resp. 55–57. But the challenged claims recite inhaled treprostinil, and, as discussed above, inhaled treprostinil is taught by each of the '212 patent, Voswinckel JESC, and Voswinckel JAHA. Ex. 1001, 18:22–44; Ex. 1006, code (57); Ex. 1007, 7; Ex. 1008, 3; Ex. 1035, 582. Patent Owner does not even allege that the results of the challenged claims are unexpected over these references.[9] Accordingly, we find that the evidence of record does not establish that the challenged claims produced a result that was unexpected over the closest prior art.

(2) Copying

Second, Patent Owner directs us to evidence that allegedly demonstrates that the challenged claims would have been nonobvious because Petitioner copied Patent Owner's product, Tyvaso, which is an embodiment of the challenged claims, when Petitioner developed its product, LIQ861. PO Resp. 57–61.

"[F]or objective indicia of nonobviousness to be accorded substantial weight, its proponent must establish a nexus between the evidence and the merits of the claimed invention." *Lectrosonics, Inc. v. Zaxcom, Inc.*, IPR2018-01129, Paper 33, 32 (PTAB Jan. 24, 2020) (precedential) (citing *ClassCo, Inc. v. Apple, Inc.*, 838 F.3d 1214, 1220 (Fed. Cir. 2016)). A patentee is entitled to a presumption of nexus "when the patentee shows that

[9] Patent Owner argues that Voswinckel JESC and Voswinckel JAHA are not prior art to the '793 patent. PO Response 44–55; Sur-Reply 2–11, 25. As discussed above, however, Petitioner has shown by a preponderance of the evidence that these references qualify as prior art.

the asserted objective evidence is tied to a specific product and that product 'embodies the claimed features, and is coextensive with them.'" *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (quoting *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018) (quoting *Brown & Williamson Tobacco Corp. v. Philip Morris Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000))).

Here, Patent Owner does not allege, let alone "show[]" as required by *Fox Factory*, that Petitioner's LIQ861 product "is coextensive with" the features claimed in the '793 patent. 944 F.3d at 1373; *see* PO Resp. 57–61; Sur-Reply 26. Patent Owner does allege that the LIQ861 product embodies the challenged claims, PO Resp. 58–61, and we presume for purposes of our analysis that Patent Owner's allegation on this issue is correct. But *Fox Factory* requires both a showing that the product in question embodies the claims and a showing that the product in question is coextensive with the claims, and Patent Owner satisfies at most one of those two requirements. Accordingly, we find that a presumption of nexus is inappropriate.

"A finding that a presumption of nexus is inappropriate does not end the inquiry into secondary considerations." *Fox Factory*, 944 F.3d at 1373. "To the contrary, the patent owner is still afforded an opportunity to prove nexus by showing that the evidence of secondary considerations is the 'direct result of the unique characteristics of the claimed invention.'" *Id.* at 1373–74 (quoting *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996)). "Where the offered secondary consideration actually results from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention," meaning that "there must be a nexus to

some aspect of the claim not already in the prior art." *In re Kao*, 639 F.3d 1057, 1068–69 (Fed. Cir. 2011) (emphasis in original).

On the other hand, there is no requirement that "objective evidence must be tied exclusively to claim elements that are not disclosed in a particular prior art reference in order for that evidence to carry substantial weight." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1331 (Fed. Cir. 2016). A patent owner may show, for example, "that it is the claimed combination as a whole that serves as a nexus for the objective evidence; proof of nexus is not limited to only when objective evidence is tied to the supposedly 'new' feature(s)." *Id.* Ultimately, the fact finder must weigh the secondary considerations evidence presented in the context of whether the claimed invention as a whole would have been obvious to a skilled artisan. *Id.* at 1331–32.

Here, Patent Owner directs us to several pieces of evidence that it contends show the LIQ861 product has a nexus to the challenged claims. First, as noted above, Patent Owner argues that LIQ861 embodies those claims. PO Resp. 58–61. Second, Patent Owner notes that "[t]he pharmacokinetics and bioavailability of a 79.5 microgram capsule dose [of LIQ861] was directly compared [by Petitioner] with Patent Owner's commercial product," demonstrating that "Petitioner's commercial product had comparable treprostinil bioavailability with Tyvaso® when delivered in a similar dosage range." *Id.* at 57–58 (citing Ex. 2085). Third, Patent Owner directs us to the new drug application Petitioner filed with the FDA, "relying in part on FDA's previous findings of efficacy and safety of Tyvaso® for the treatment of PAH." *Id.* at 58 (citing Ex. 2089, 3).

Taking these pieces of evidence in reverse order, we note first that the new drug application for LIQ861 was filed "under the 505(b)(2) regulatory pathway." *Id.*; *see also* Reply 25; Ex. 2089, 3. As Petitioner notes, Reply 25, and as Patent Owner does not dispute, Sur-Reply 26, applications for drugs under this pathway do not necessarily copy all aspects of the original drug, but they may rely on the investigations that showed the safety and efficacy of the original drug that uses the same active ingredient. 21 U.S.C. § 355(b)(2). In this respect, they differ from applications under the § 505(j) regulatory pathway, under which the new drug must generally have the same "active ingredient," "route of administration," "dosage form," "strength," and "labeling" as the original drug. 21 U.S.C. § 355(j)(2). Because the challenged claims here recite limitations requiring administration by inhalation of a particular amount of treprostinil in a particular number of breaths (and in some cases using a particular type of device and with the drug in a particular form), evidence that Petitioner merely relied on previous studies of the safety and efficacy of the recited active ingredient is not particularly strong evidence of copying.

Next, we consider the evidence that Petitioner compared the pharmacokinetics and bioavailability of its LIQ861 product with those of Patent Owner's Tyvaso product. Ex. 2085. Patent Owner argues that this evidence shows that "Petitioner's commercial product had comparable treprostinil bioavailability with Tyvaso® when delivered in a similar dosage range." PO Resp. 57–58. Regardless of whether an objective indicium of nonobviousness has its nexus to a single "aspect of the claim not already in the prior art," *Kao*, 639 F.3d at 1068–69, or to "the claimed combination as a whole," *WBIP*, 829 F.3d at 1331, it still must have some nexus to the claim

in question. The challenged claims, however, do not recite any limitations for treprostinil bioavailability or pharmacokinetics. Ex. 1001, 18:22–44. Accordingly, evidence that Petitioner formulated its product to have similar bioavailability and pharmacokinetics to Patent Owner's product is, at most, very weak evidence of copying as to the claims at issue here.

Finally, we consider the evidence that LIQ861 embodies the challenged claims. PO Resp. 58–61. "Not every competing product that arguably falls within the scope of a patent is evidence of copying; otherwise, 'every infringement suit would automatically confirm the nonobviousness of the patent.'" *Wyers v. Master Lock Co.*, 616 F.3d 1231, 1246 (quoting *Iron Grip Barbell Co., Inc. v. USA Sports, Inc.*, 392 F.3d 1317, 1325 (Fed. Cir. 2004)). Proof of copying requires "actual evidence of copying efforts as opposed to mere allegations regarding similarities between the accused product and a patent." *Liqwd, Inc. v. L'Oreal USA, Inc.*, 941 F.3d 1133, 1137–38 (Fed. Cir. 2019). Thus, evidence that LIQ861 embodies the challenged claims is not evidence that could, without more, support a finding that Petitioner copied Patent Owner's patented method. As discussed above, to the extent there is any evidence of what *Liqwd* refers to as "copying efforts" beyond mere similarity between LIQ861 and the challenged claims, that evidence shows that Petitioner copied only features that appear in the prior art, are not recited in the challenged claims, or both. Accordingly, we do not find that Patent Owner has shown that Petitioner copied the method of the challenged claims.

(3) Long-Felt and Unmet Need

Patent Owner directs us to evidence that allegedly demonstrates that the challenged claims would have been nonobvious because "[t]he claimed

invention of the '793 patent satisfies a long-felt unmet need in the treatment of pulmonary hypertension." PO Resp. 61–62; *see* Sur-Reply 26. Patent Owner relies on three separate theories to demonstrate this long-felt need. First, in the Response, Patent Owner argues that the approval of inhaled treprostinil as the first treatment for "pulmonary hypertension associated with interstitial lung disease" satisfied "a completely unmet medical need." PO Resp. 61–62 (quoting Ex. 2056, 105:6–8). Second, also in the Response, Patent Owner argues that Petitioner admitted that its LIQ861 product "fulfill[ed] a significant unmet need for PAH patients by maximizing the therapeutic benefits of treprostinil by safely delivering doses to the lungs in 1 to 2 breaths using a discreet, convenient, easy-to-use inhaler." *Id.* at 62 (quoting Ex. 2085). Third, in the Sur-Reply, Patent Owner argues that its Tyvaso product satisfied a need for an "inhaled treatment for pulmonary hypertension" that avoided the "inconvenient dosing and side effects of Ventavis," the only previously approved treatment. Sur-Reply 26 (citing Ex. 1002 ¶ 42; Ex. 1108, 44:19–21, 49:17–50:10; Ex. 2055, 28:22–29:20). Each of these arguments fails for a different reason.

We begin with Patent Owner's third argument, that Tyvaso satisfied a need for an inhaled treatment that avoided the dosing problems and side effects of Ventavis. Patent Owner offers this argument for the first time in the Sur-Reply. *Id.* "A sur-reply may only respond to arguments raised in the corresponding reply." 37 C.F.R. § 42.23(b). "'Respond,' in the context of 37 C.F.R. § 42.23(b), does not mean proceed in a new direction with a new approach as compared to the positions taken in a prior filing." Patent Trial and Appeal Board Consolidated Trial Practice Guide 74 (Nov. 2019), available at https://www.uspto.gov/sites/default/files/documents/tpgnov.pdf.

As discussed in more detail below, in its prior filings, Patent Owner's only positions with respect to long-felt need were (1) that the patented method satisfied a need for a treatment for pulmonary hypertension associated with interstitial lung disease and (2) that Petitioner admitted that its product satisfied a need. PO Resp. 61–62. Neither of those positions related to a need for a treatment that avoided the problems associated with Ventavis. *Id.* Accordingly, Patent Owner's argument in the Sur-Reply is a new argument that we do not consider further.

Next, we consider Patent Owner's argument that the method of the '793 patent provided the first treatment for pulmonary hypertension associated with interstitial lung disease. *Id.* Even if this is true, it is extremely weak evidence of the nonobviousness of the claims at issue because those claims do not cover treatment of pulmonary hypertension associated with interstitial lung disease. There are multiple groups of pulmonary hypertension conditions. Ex. 1088, 1. In addition to other groups not relevant here, these groups include "WHO Group 1," or "[p]ulmonary arterial hypertension," and "WHO Group 3," or "[p]ulmonary hypertension associated with interstitial lung disease." *Id.* Patent Owner's declarant, Dr. Waxman, testifies that all pulmonary hypertension groups other than Group 1 fall outside the scope of the claims of the '793 patent. Ex. 1132, 116:9–119:12. Dr. Hill agrees. Ex. 1106 ¶ 100. Thus, to the extent the challenged claims satisfied a long-felt and unmet need for a treatment for pulmonary hypertension associated with interstitial lung disease, Patent Owner has not shown that that need is tied to any limitation of the challenged claims or to any challenged claim as a whole.

Finally, we consider Patent Owner's argument that Petitioner admitted that its LIQ861 product "fulfill[ed] a significant unmet need for PAH patients by maximizing the therapeutic benefits of treprostinil by safely delivering doses to the lungs in 1 to 2 breaths using a discreet, convenient, easy-to-use inhaler." PO Resp. 62 (quoting Ex. 2085). "Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer that the need would not have persisted had the solution been obvious." *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1056 (Fed. Cir. 2016). Patent Owner directs us to two pieces of evidence. First, Patent Owner directs us to Exhibit 2085, which states that LIQ861 "fulfill[ed] a significant unmet need for PAH patients by maximizing the therapeutic benefits of treprostinil by safely delivering doses to the lungs in 1 to 2 breaths using a discreet, convenient, easy-to-use inhaler." Ex. 2085, 1. This demonstrates that Petitioner believed its product satisfied a particular "significant unmet need," but it does not demonstrate how long that need persisted. *Id.* Second, Patent Owner directs us to page F-7 of Exhibit 2089, but this page does not address the filling of any need by LIQ861. Ex. 2089, F-7. Thus, Patent Owner does not show that any previously unmet need satisfied by LIQ861 was a need that had persisted, as required by *Apple v. Samsung*. Accordingly, we do not find that Patent Owner has shown that the patented method satisfied any previously unmet and long-felt need.

d. Dependent Claims

Claims 2–8 of the '793 patent depend directly or indirectly from claim 1. Ex. 1001, 18:32–45. Petitioner argues that the combination of the '212 patent, Voswinckel JESC, and Voswinckel JAHA teaches or suggests

the additional limitations of these claims. Pet. 41–46. Patent Owner does not dispute these arguments, except with respect to claims 4, 6, and 7. PO Resp. 38–40.

We have reviewed the evidence cited by Petitioner with respect to dependent claims 2, 3, 5, and 8, and we are persuaded that Petitioner has shown by a preponderance of the evidence that the combination of the '212 patent, Voswinckel JESC, and Voswinckel JAHA teaches or suggests the subject matter of these claims. For example, claim 2 depends from claim 1 and recites a further limitation that requires that "the inhalation device [be] a soft mist inhaler," and Petitioner directs us to evidence that soft mist inhalers were known in the prior art, as well as evidence that soft mist inhalers were known to be suitable for inhaled delivery of drugs in a small number of breaths. Ex. 1001, 7:33–39, 18:32–33; Ex. 1002 ¶¶ 106–110; Ex. 1004 ¶¶ 66–71; Ex. 1006, 5:30–32; Ex. 1034, 175.

The parties dispute the obviousness of claims 4, 6, and 7. Claim 4 depends from claim 1 and recites a limitation requiring that "the inhalation device [be] a dry powder inhaler." Ex. 1001, 18:36–37. Claim 6 depends from claim 4 and adds a limitation requiring that "the formulation [be] a powder." *Id.* at 18:40–41. Claim 7 depends from claim 6 and adds a limitation requiring that "the powder comprise[] particles less than 5 micrometers in diameter." *Id.* at 18:42–43. Petitioner argues that each of these limitations is taught or suggested by the '212 patent. Pet. 43–45 (citing Ex. 1006, 5:30–32, 5:37–41, 14:19–21; Ex. 1002 ¶¶ 116–117; Ex. 1004 ¶¶ 77–80; Ex. 1038, 311). Patent Owner argues that Petitioner's obviousness argument with respect to these claims is inconsistent with Petitioner's argument in the parallel District Court proceeding that these

claims are not enabled. PO Resp. 38–40. Specifically, Patent Owner argues that Dr. Gonda's testimony here that a person of ordinary skill in the art "would have had a reasonable expectation of success that the 'powder' disclosed and claimed in the '212 Patent could be 'inhaled' by a patient using a dry powder inhaler" contradicts Dr. Gonda's testimony in District Court that a person of ordinary skill in the art "would be unable to formulate a treprostinil powder suitable for administration via a dry powder inhaler for [pulmonary hypertension] patients without excessive experimentation." PO Resp. 38–39 (quoting Ex. 1004 ¶ 80; Ex. 2091, 40–61). Because Dr. Gonda's District Court testimony is more "lengthy" than his testimony here, Patent Owner argues that the District Court testimony is more reliable and that, accordingly, we should not rely on Dr. Gonda's testimony here. *Id.* at 40.

Dr. Gonda's testimony here provides support for Petitioner's argument that a person of ordinary skill in the art would have had a reasonable expectation of success in combining the teachings of the '212 patent, Voswinckel JESC, and Voswinckel JAHA in order to arrive at the invention of claims 4, 6, and 7. Ex. 1004 ¶ 80. Reasonable expectation of success is a separate inquiry from enablement. *UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1327 (Fed. Cir. 2018) (finding no "authority for the proposition that the presumption of" enablement of prior art "precludes . . . finding that there was no reasonable expectation of success"). Accordingly, the mere fact that Dr. Gonda testifies to a lack of enablement in one forum and to the presence of a reasonable expectation of success in a second forum does not render unreliable the testimony in either forum. Therefore, we credit the unrebutted testimony of Dr. Gonda that a

person of ordinary skill in the art "would have had a reasonable expectation of success that the 'powder' disclosed and claimed in the '212 Patent could be 'inhaled' by a patient using a dry powder inhaler." Ex. 1004 ¶ 80. In addition, Dr. Gonda's testimony in this proceeding is supported by a citation to Ex. 1038, an October 2005 article that states that dry powder inhalers "are a widely accepted inhaled delivery dosage form," as well as to Ex. 1019, an article stating that 14 separate dry powder inhalers were approved in the United States by 2006. Ex. 1019, 33; Ex. 1038, 1311. This evidence provides us with an additional reason to credit Dr. Gonda's testimony as to reasonable expectation of success.

Moreover, even if there were some connection between enablement and reasonable expectation of success, Patent Owner concedes that the '212 patent enables its own claims. Tr. 43:6–50:9. In other words, the '212 patent provides enough information for a person of ordinary skill in the art to have made and used the invention defined by the claims of the '212 patent. *See* 35 U.S.C. § 112. That invention includes "[a] method for treating pulmonary hypertension in a mammal comprising delivering to said mammal an effective amount of [treprostinil] or its pharmaceutically acceptable salt or ester by inhalation," wherein the treprostinil "is inhaled in powder form comprising particles less than 10 micrometers in diameter." Ex. 1006, 14:9–12, 14:19–21. To the extent that, despite *UCB*, 890 F.3d at 1327, there remains any connection at all between a reasonable expectation of success and enablement, the fact that a person of ordinary skill in the art was enabled to make and use this invention presumably would have rendered that person more likely to expect success in achieving the similar invention of claims 4, 6, and 7 of the '793 patent.

Further, as discussed above with respect to the reason to combine the teachings of the '212 patent, Voswinckel JESC, and Voswinckel JAHA, Petitioner directs us to other evidence that a person of ordinary skill in the art would have had a reasonable expectation of success.

For all these reasons, we determine that Petitioner has shown by a preponderance of the evidence that a person of ordinary skill in the art would have had a reason to combine the teachings of the '212 patent, Voswinckel JESC, and Voswinckel JAHA and would have had a reasonable expectation of success in doing so in order to arrive at the invention of the challenged claims, including claims 4, 6, and 7.

Thus, we move on to whether the prior art teaches or suggests the additional limitations of claims 4, 6, and 7. Petitioner argues that the '212 patent teaches or suggests each of these limitations, and Patent Owner does not dispute that argument. Pet. 43–45; PO Resp. 38–40. Claim 4 recites a limitation requiring that "the inhalation device [be] a dry powder inhaler." Ex. 1001, 18:36–37. The '212 patent teaches using an "inhaler" to deliver treprostinil, that "solid formulations, usually in the form of a powder, may be inhaled in accordance with the present invention," and that treprostinil "is inhaled in powder form." Ex. 1006, 5:30–32, 5:37–39, 14:19–21. Dr. Hill testifies that a person of ordinary skill in the art would have known that the "inhaler" used to deliver the "powder" of the '212 patent was a dry powder inhaler. Ex. 1002 ¶ 116. Claim 6 depends from claim 4 and adds a limitation requiring that "the formulation [be] a powder." Ex. 1001, 18:40–41. The '212 patent teaches that "solid formulations, usually in the form of a powder, may be inhaled in accordance with the present invention," as well as that treprostinil "is inhaled in powder form." Ex. 1006, 5:37–39, 14:19–

21. Claim 7 depends from claim 6 and adds a limitation requiring that "the powder comprise[] particles less than 5 micrometers in diameter." Ex. 1001, 18:42–43. The '212 patent teaches that "the particles are preferably less than 10 micrometers in diameter, and more preferably, less than 5 micrometers in diameter." Ex. 1006, 5:39–41. Accordingly, Petitioner has shown by a preponderance of the evidence that the '212 patent teaches or suggests the additional limitations of claims 4, 6, and 7 of the '793 patent.

e. Conclusion

As discussed above, Petitioner has shown by a preponderance of the evidence that the combination of the '212 patent, Voswinckel JESC, and Voswinckel JAHA teaches or suggests the subject matter of claims 1–8. Petitioner also has shown by a preponderance of the evidence that a person of ordinary skill in the art would have had a reason to combine the teachings of the '212 patent, Voswinckel JESC, and Voswinckel JAHA and would have had a reasonable expectation of success in doing so to arrive at the invention of the challenged claims. In addition, the preponderance of the evidence shows that there is at most very weak evidence of objective indicia of nonobviousness, including unexpected results, copying, and long-felt but unmet need. Weighing together the evidence of the prior art teaching or suggesting the subject matter of the claims, of a reason to combine the teachings of the prior art with a reasonable expectation of success, and of objective indicia of nonobviousness, we conclude that Petitioner has demonstrated that claims 1–8 of the '793 patent would have been obvious over the combination of the '212 patent, Voswinckel JESC, and Voswinckel JAHA and, accordingly, that those claims are unpatentable.

C. Asserted Obviousness over '212 Patent and Voswinckel JESC

Petitioner argues that claims 1–8 would have been obvious over the combination of the '212 patent and Voswinckel JESC. Pet. 46–50. Because Petitioner has shown by a preponderance of the evidence that all of the challenged claims would have been obvious over the similar combination of the '212 patent, Voswinckel JESC, and Voswinckel JAHA, we need not reach this asserted ground.

D. Grounds Relying on Ghofrani or Voswinckel 2006

Petitioner argues that claim 1 was anticipated by Ghofrani; that claims 1, 3, and 8 would have been obvious over the combination of Voswinckel JAHA and Ghofrani; that claims 1 and 3 were anticipated by Voswinckel 2006; and that claims 2 and 4–8 would have been obvious over the combination of Voswinckel 2006 and the '212 patent. Pet. 50–64. Patent Owner argues that each of these grounds fails because Petitioner fails to show sufficiently that Ghofrani and Voswinckel 2006 qualify as prior art. PO Resp. 44–54. Petitioner disagrees, arguing that these references qualify as prior art under 35 U.S.C. § 102(a). Pet. 25–30.

In the institution decision, we determined that, on the preliminary record available at the time, Petitioner had not shown that either Ghofrani or Voswinckel 2006 qualified as prior art. Inst. Dec. 37–43. Since that decision, Petitioner has neither supplemented the record nor made any additional arguments on this issue. Reply 1–27. During the hearing, Petitioner did not agree that it had abandoned its argument on the grounds asserting Ghofrani or Voswinckel 2006. Tr. 35:13–36:10. Nevertheless, in the absence of any new evidence or argument, we have been directed to nothing that persuades us to reach any decision other than we reached

initially. Accordingly, our analysis below mirrors the analysis we conducted in the institution decision.

1. Prior-Art Status of Ghofrani

Ghofrani is an article published in the German journal Herz in June 2005, less than one year before the priority date of the '793 patent. Pet. 25; Ex. 1010, 9; Ex. 1036 ¶¶ 47–55. Petitioner argues that Ghofrani is prior art to the '793 patent under 35 U.S.C. § 102(a). Pet. 25–27. Patent Owner disagrees, arguing that Petitioner has not shown sufficiently that Ghofrani is "by others" under § 102(a). PO Resp. 44–51.

As both parties acknowledge, establishing prior-art status under § 102(a) requires showing that the reference is "by others," meaning that it was authored by an entity different from the entity that invented the challenged patent. Pet. 26–27; PO Resp. 44–46; *see Lacks Industries, Inc. v. McKechnie Vehicle Components USA, Inc.*, 322 F.3d 1335, 1346 (Fed. Cir. 2003) ("it is well-settled law that an inventor's own disclosure will not anticipate his later invention" unless published more than one year prior to the priority date (internal quotation marks omitted)).

The authors of Ghofrani are "Hossein Ardeschir Ghofrani, Robert Voswinckel, Frank Reichenberger, Friedrich Grimminger, [and] Werner Seeger." Ex. 1010, 9. The inventors of the '793 patent are Horst Olschewski, Robert Roscigno, Lewis J. Rubin, Thomas Schmehl, Werner Seeger, Carl Sterritt, and Robert Voswinckel. Ex. 1001, code (72). Thus, there are, as Petitioner argues, "inventors listed on the '793 Patent that are not listed as authors on Ghofrani, and vice versa." Pet. 26. Specifically, Ghofrani, Reichenberger, and Grimminger authored the Ghofrani reference but were not inventors of the '793 patent; and Olschewski, Roscigno, Rubin,

Schmehl, and Sterritt were inventors of the '793 patent but not authors of the Ghofrani reference.

Petitioner argues that these differences alone are sufficient to show that Ghofrani is "by others." *Id.* at 26–27. We agree that it is possible, depending on the state of the rest of the evidence of record, for any difference between the authors of an alleged prior-art reference and the inventors of a challenged patent to render the reference "by others" for purposes of § 102(a). *See, e.g.*, *In re Katz*, 687 F.2d 450, 455 (CCPA 1982) ("ambiguity [was] created by the printed publication" where authors included people not named as inventors); *cf. In re Land*, 368 F.2d 866, 877 (CCPA 1966) (for purposes of § 102(e), reference authored by one co-inventor was "by another").

That said, it is not always sufficient for Petitioner merely to show a difference between a list of authors and a list of inventors. Where the record contains evidence that the reference was derived entirely from the work of the inventors or at least one joint inventor, this evidence may be sufficient to show that the reference is not "by others" for purposes of § 102(a). *Katz*, 687 F.2d at 455–56 (finding inventor's declaration of sole inventorship sufficient to render reference authored by inventor and others not "by others"). Although the testimony of an inventor that the reference in question was derived from the inventors' work may be sufficient on its own, at least where it is not "a mere pro forma restatement of the oath in [the inventor's] application," affidavits from the other authors disclaiming the invention are particularly strong evidence that the reference is not "by others." *Id.* ("Submission of such affidavits or declarations would have ended the inquiry . . . ."). Here, for the reasons discussed below, the

preponderance of the evidence persuades us that, despite the differences between its list of authors and the list of the inventors of the '793 patent, Ghofrani is not "by others" for purposes of § 102(a).

Petitioner's first argument that Ghofrani is "by others" is that there are people who are authors of Ghofrani who are not inventors of the '793 patent. Pet. 26. But Dr. Seeger, one of the inventors of the '793 patent, as well as an author of Ghofrani, describes the roles of the other authors of Ghofrani, explaining that Dr. Ghofrani drafted the portion of the article "relating to phosphodiesterase inhibitors," that Drs. Reichenberger and Grimminger drafted the portion of the article relating to "the use of selective endothelin A receptor agonists for treating pulmonary hypertension," and that he and Dr. Voswinckel—another co-inventor—drafted the portion of the article relating to "the use of inhaled iloprost and inhaled treprostinil for treatment of pulmonary hypertension," the only portion on which Petitioner's unpatentability case rests. Ex. 2003 ¶¶ 4–8. Dr. Seeger's testimony is corroborated by the testimony of Drs. Ghofrani, Reichenberger, and Grimminger, each of whom testifies that they "did not make material contributions to" the portion of the Ghofrani reference relating to inhaled treprostinil. Ex. 2004 ¶¶ 4–5; Ex. 2005 ¶¶ 4–5; Ex. 2006 ¶¶ 4–5. This is precisely the type of testimony that the *Katz* court held should "end[] the inquiry" into whether Ghofrani was "by others." 687 F.2d at 455–56. Accordingly, this evidence overcomes Petitioner's argument that the difference between the Ghofrani authors and the inventors of the '793 patent is sufficient to show that Ghofrani is "by others."

Petitioner also argues that the failure to include some of the inventors of the '793 patent—Olschewski, Roscigno, Rubin, Schmehl, and Sterritt—as

authors of Ghofrani renders Ghofrani "by others." Pet. 26–27. But "the fact that a reference does not list any co-inventors as authors . . . is certainly not dispositive in itself." *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 969 (Fed. Cir. 2014); *see* MPEP § 2132.01(I) ("An inventor's or at least one joint inventor's disclosure of his or her own work within the year before the application filing date cannot be used against the application as prior art under pre-AIA 35 U.S.C. 102(a)."). Moreover, Dr. Seeger explains the roles of the other named inventors in designing trials and clinical studies leading to the patent application. Ex. 2003 ¶¶ 22–27. In particular, Dr. Seeger testifies that the Ghofrani reference did not report on the details of the studies and trials that were in part designed by these other authors, explaining why they did not contribute to writing Ghofrani, even though they were involved in the related work that gave rise to the '793 patent. *Id.* ¶¶ 11–12. Dr. Seegar further explains that, "any study that formed the basis of our discussion of inhaled trepostinil in [Ghofrani and two other references] was performed by me in conjunction with my ongoing collaboration with Drs. Voswinckel, Olschewski, Rubin, Schmehl, Sterrit, and Roscigno." *Id.* ¶ 12. Again, then, the preponderance of the evidence supports a determination that Ghofrani is not "by others" for purposes of § 102(a).

2. Prior-Art Status of Voswinckel 2006

The issues and arguments regarding Voswinckel 2006 are quite similar to those discussed above regarding Ghofrani. Petitioner argues that Voswinckel 2006 qualifies as prior art under § 102(a) and that it is "by others" both because some of its authors—specifically, Ghofrani and Grimminger—are not inventors of the '793 patent and because some

inventors of the '793 patent—specifically, Olschewski, Roscigno, Rubin, Schmehl, and Sterritt—are not authors of Voswinckel 2006. Pet. 27–30. Patent Owner disagrees, pointing to the testimony of Drs. Seeger, Ghofrani, and Grimminger explaining the role that the other inventors of the '793 patent played, as well as making clear that neither Ghofrani nor Grimminger authored the portion of Voswinckel 2006 that is relevant as prior art. PO Resp. 44–46, 51–54; Ex. 2003 ¶¶ 20–21 (describing the roles of Drs. Ghofrani and Grimminger, explaining that they "did not participate in the design of any of the studies, did not select the dosing regimen, and did not conduct analysis of patient results discussed in . . . Voswinckel 2006"); 19 ("any study that formed the basis of our discussion of inhaled treprostinil in this reference was performed by me in connection with my ongoing collaboration with [the other inventors]").

For the same reasons discussed above with respect to Ghofrani, we determine that the preponderance of the evidence shows that Petitioner has not shown sufficiently that Voswinckel 2006 is "by others."

3. Conclusion

For the reasons discussed above, Petitioner has not shown that either Ghofrani or Voswinckel 2006 qualifies as prior art. Accordingly, Petitioner has not shown the unpatentability of any challenged claim on any ground that relies on either Ghofrani or Voswinckel 2006.

E. Motions to Exclude Evidence

Each party filed a motion to exclude evidence. Paper 65; Paper 66. We consider each motion separately below.

1. Petitioner's Motion to Exclude

Petitioner moves to exclude Exhibits 2092, 2100, 2101, 2102, and 2103 as not authenticated and, for Ex. 2092, as incomplete. Paper 65, 1. Petitioner also moves to exclude the portions of Patent Owner's Sur-Reply that rely on these exhibits. *Id.*

We do not rely on any of the exhibits Petitioner challenges in reaching our decision in this case. Accordingly, we dismiss Petitioner's motion to exclude as moot.

2. Patent Owner's Motion to Exclude

Patent Owner moves to exclude Exhibits 1037, 1114, 1117, and 1120 as hearsay and, for Ex. 1037, as not authenticated, irrelevant, and lacking the original writing. Paper 66, 2. Patent Owner also moves to exclude Exhibits 1029, 1050, 1066, 1074, and 1078 as not authenticated. *Id.* Patent Owner moves to exclude Exhibit 1087 as lacking personal knowledge and as irrelevant. *Id.* Patent Owner also moves to exclude portions of Exhibit 1112 as not based on sufficient facts and analysis. *Id.* Further, Patent Owner moves to exclude the portions of Petitioner's Petition and Reply, as well as the portions of Exhibits 1002 and 1004, that cite these exhibits. *Id.* at 2–3.

We do not rely on any of the exhibits or portions of exhibits Patent Owner moves to exclude in reaching our decision in this case, with two exceptions: paragraphs 36 and 42 of Ex. 1002, which cite Ex. 1029, and paragraph 56 of Ex. 1004, which Patent Owner argues cites Ex. 1029, Ex. 1050, and Ex. 1066. We dismiss as moot Patent Owner's motion to exclude, except as to these paragraphs of Exhibits 1002 and 1004. We discuss the remaining portions of Patent Owner's motion to exclude below.

a. Paragraphs 36 and 42 of Exhibit 1002

Patent Owner moves to exclude paragraphs 36 and 42 of Exhibit 1002 because they rely on Exhibit 1029, which Patent Owner argues lacks authentication. Paper 66, 2–3.

Certain items are self-authenticating under Federal Rule of Evidence ("FRE") 902, and, for items that are not self-authenticating, FRE 901 provides that "the proponent [of the evidence in question] must produce evidence sufficient to support a finding that the item is what the proponent claims it is." Fed. R. Evid. 901(a). The evidence showing "that the items is what the proponent claims it is" may include "[t]estimony that an item is what it is claimed to be," or "[t]he appearance, contents, substance, internal patterns, or other distinctive characteristics of the item, taken together with all the circumstances," among other things. Fed. R. Evid. 901(b).

Here, Dr. Hill, Petitioner's declarant, testifies three times that Exhibit 1029 is the "Ventavis Label 2004." Ex. 1002 ¶¶ 36, 41, 42. Dr. Gonda, another declarant for Petitioner, testifies that Exhibit 1029 is the "Ventavis (iloprost) Label." Ex. 1004 ¶ 56 n.4. Dr. Waxman, Patent Owner's declarant, cites to Exhibit 1029 twice as support for the approved dose for, and side effects experienced by, patients taking Ventavis. Ex. 2052 ¶ 100. The "appearance, contents, substance, internal patterns, [and] other distinctive characteristics," Fed. R. Evid. 901(b), of Ex. 1029 confirm the testimony of Drs. Hill, Gonda, and Waxman. The document contains sections titled "description," "clinical pharmacology," "indications and usage," "contraindications," "warnings," "precautions," "adverse reactions," "overdosage," "dosage and administration," "how supplied," "storage," and "patient information," with each section providing information related to

"Ventavis." Ex. 1029, 1–17. This information is consistent with a drug label for Ventavis, which is what Dr. Hill and Dr. Gonda testify, what Dr. Waxman assumes, and what Petitioner argues, Ex. 1029 is. Accordingly, we find that Petitioner has "produce[d] evidence sufficient to support a finding that [Ex. 1029] is what [Petitioner] claims it is." Fed. R. Evid. 901(a). Because Ex. 1029 does not lack authentication, we deny Patent Owner's motion to exclude paragraphs 36 and 42 of Ex. 1002, which cite to Ex. 1029.

b. Paragraph 56 of Exhibit 1004

Patent Owner moves to exclude paragraph 56 of Exhibit 1004 because it relies on Exhibits 1029, 1050, and 1066, all of which Patent Owner argues lack authentication. Paper 66, 2–3. We discuss Exhibit 1029 above, finding that it is sufficiently authenticated. The situation with respect to Exhibits 1050 and 1066 is similar. Dr. Gonda testifies that Ex. 1050 is the "Pulmozyme® Label" and that Ex. 1066 is the "AccuNeb® Label." Ex. 1004 ¶ 56 n.4. Moreover, Dr. Gonda's testimony about what Exhibits 1050 and 1066 are is confirmed by the contents of those exhibits. Exhibit 1050 contains sections titled "description," "clinical pharmacology," "indications and usage," "contraindications," "warnings," "precautions," "adverse reactions," "overdosage," "dosage and administration," and "how supplied," with each section providing information related to "Pulmozyme." Ex. 1050, 1–2. Exhibit 1066 contains sections titled "description," "clinical pharmacology," "indications and usage," "contraindications," "warnings," "precautions," "adverse reactions," "overdosage," "dosage and administration," "how supplied," "storage," and "patient's instructions for use," with each section providing information related to "AccuNeb."

Ex. 1066, 1–2. This information is consistent with drug labels for Pulmozyme and AccuNeb, which is what Dr. Gonda testifies, and what Petitioner argues, Exhibits 1050 and 1066 are. Accordingly, we find that Petitioner has "produce[d] evidence sufficient to support a finding that [Ex. 1050 and Ex. 1066 are] what [Petitioner] claims [they are]." Fed. R. Evid. 901(a). Because Exhibits 1050 and 1066 do not lack authentication, we deny Patent Owner's motion to exclude paragraph 56 of Ex. 1004, which cites to those exhibits.

CONCLUSION[10]

For the reasons discussed above, Petitioner has shown by a preponderance of the evidence that claims 1–8 of the '793 patent are unpatentable.

Claims	35 U.S.C. §	Reference(s)/Basis	Claims Shown Unpatentable	Claims Not Shown Unpatentable
1–8	103(a)	'212 patent, Voswinckel JESC, Voswinckel JAHA	1–8	
1–8	103(a)	'212 patent, Voswinckel JESC[11]		
1	102(a)	Ghofrani		1
1, 3, 8	103(a)	Voswinckel JAHA, Ghofrani		1, 3, 8
1, 3	102(a)	Voswinckel 2006		1, 3
2, 4–8	103(a)	Voswinckel 2006, '212 patent		2, 4–8
Overall Outcome			1–8	

[10] Should Patent Owner wish to pursue amendment of the challenged claims in a reissue or reexamination proceeding subsequent to the issuance of this Decision, we draw Patent Owner's attention to the April 2019 Notice Regarding Options for Amendments by Patent Owner Through Reissue or Reexamination During a Pending AIA Trial Proceeding. *See* 84 Fed. Reg. 16,654 (Apr. 22, 2019). If Patent Owner chooses to file a reissue application or a request for reexamination of the challenged patent, we remind Patent Owner of its continuing obligation to notify the Board of any such related matters in updated mandatory notices. *See* 37 C.F.R. §§ 42.8(a)(3), (b)(2).

[11] This Final Written Decision does not reach these grounds because Petitioner has proven all challenged claims are unpatentable based on obviousness over the combination of the '212 patent, Voswinckel JESC, and Voswinckel JAHA.

ORDER

It is hereby

ORDERED that, based on the preponderance of the evidence, claims 1–8 of the '793 patent have been shown to be unpatentable;

FURTHER ORDERED that Petitioner's Motion to Exclude is dismissed as moot;

FURTHER ORDERED that Patent Owner's Motion to Exclude is denied as to paragraphs 36 and 42 of Exhibit 1002 and as to paragraph 56 of Exhibit 1004;

FURTHER ORDERED that Patent Owner's Motion to Exclude is dismissed as moot in all other respects; and

FURTHER ORDERED that, because this is a Final Written Decision, parties to this proceeding seeking judicial review of this Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

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IPR2021-00406
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